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Trends in survival from oesophageal cancer in Switzerland

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SCHWEIZER KREBSBULLETIN
BULLETIN SUISSE DU CANCER
DU CANCER

RAUCHEN TÖTET
Philip Morris versus Uruguay

Titelbild:
Pressespiegel, S. 187

Gynäkologische Tumoren

Fotos aus Portugal von Alessandro Amitrano, Locarno

Schwerpunktthema Ausgabe Nr. 4-2014: Cancer Survivors

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Significant changes in the management of gynecological cancers

Over the last 30 years significant changes have been achieved in the management of epithelial ovarian cancer leading to a 2-year improvement in median overall survival. According to International Federation of Gynecology and Obstetrics (FIGO) the 5-year survival has increased from 26.8% (1985) to 49.7% (2001) while according to the Surveillance Epidemiology and End Results (SEER) program of the NCI it has improved from 36.6% (1975) to 44.6% (2010). However, still fewer than 25% of patients with ovarian cancer will survive long-term and will be cured, the gain in median survival being due to an extension of the survival time rather than an increase in the overall cure rate. Increase in overall survival is related to a variety of factors, ranging from more high-quality aggressive initial surgery to active new drugs and combinations, repeated treatments and rational planning of subsequent on /off therapy periods.

More recently, the understanding that ovarian cancer is not a single entity but many diseases with different histologies and molecular features has led to the development of personalized medicine (1). Because of the rarity of the diagnosis, targeting histology-specific pathways, such as low grade serous/endometrioid with pathway specific agents (like MEK inhibitors in advanced low-grade disease), has been successfully pursued in histology specific trials, which are necessarily multicentric and international (2). The integrated genomic analyses of 316 high-grade serous ovarian cancer (HGS-OvCa) in The Cancer Genome Atlas (TCGA) has confirmed the high prevalence of TP53 mutations and of somatic mutations. Moreover, it has showed that BRCA1/2 mutated cases have better survival than wild-type patients and that homologous recombination defects may be present in approximately half of HGS-OvCa cases (3). These data further supported the development of the synthetic lethality approach and the broader clinical evaluation of PARP inhibitors, which are today the most significant achievement of precision medicine in HGS-OvCa (4).

Can a biological process like angiogenesis be a target for treatment? So far, the lack of reproducible biomarkers to identify the patients most likely to respond to antiangiogenics has hindered the achievement of long-term significant results. Recently the Scottish Group identified, by a 63-gene signature in a subset of cases treated in the ICON 7 study, three major subgroups of patients, two with angiogenic gene upregulation (the proangiogenic groups) and one with angiogenic gene repression and immune gene upregulation (the immune molecular subgroup) (5). The latter had a significantly longer progression free survival (PFS) and overall survival possibly in relation to a more indolent disease with less blood supply and an active engagement of the tumor by the host immune system. When bevacizumab was added to the treatment, the immune subgroup showed a significantly worse PFS suggesting that a gene signature for bevacizumab might become a stratification factor.

Over the past decade it has become clear that also endometrial cancer, the most common gynecological malignancy, includes many biologically and genetically different diseases. Besides the traditional classification of Type I and Type II cancers, based on clinical, endocrine and histopathological characteristics, today a newer genomic classification on genetic and histopathological characteristics, based on the genomic

and transcriptomic analysis of the TCGA, is being discussed (6). A data set of 373 endometrial cancers (namely 307 endometrioid and 53 serous) were analyzed by next-generation sequencing technologies leading to the identification of four genomic classes: POLE (ultramutated with favorable outcome), microsatellite instable (MSI hypermutated) endometrioid, copy-number low (endometrioid) and copy-number high (serous like) with poor outcome.

Overall, it appears that endometrial cancer is a disease with many aspects and that the traditional histology-based classification only partly encompasses this heterogeneity. The genomic classification might become a stratification factor and might identify poor-risk endometrioid patients more likely to respond to specific drugs (7). The prognostic and, above all, the predictive value of the genomic classification can be assessed only through biomarker-driven clinical trials, which could become a priority considering that around 75% of patients are stages I-II and that, in this group, the outcome of women with serous and high-grade endometrioid type is still poor.

In cervical cancer, the introduction of the HPV vaccination as well as the new techniques of screening will likely eliminate the disease in vaccinated women while decreasing the mortality in the unvaccinated ones, if adequate infrastructures, information and financial resources are made available (8). Personalized medicine is still at its beginning. It is however remarkable that the only significant results so far achieved with molecule targeted agents, namely the longer overall survival in locally advanced/recurrent disease observed when bevacizumab was added to combination chemotherapy, have a sound preclinical rationale, possibly related to the overexpression of oncogenic HPV subtypes and the accumulation of HIF-1α and VEGF expression (9).

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SCHWEIZER KREBS-BULLETIN
SUISSE DU CANCER

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Strained NHS misses target on cancer care for first time

Patients in need of urgent cancer treatment are being kept waiting for too long because of a «huge strain» on the NHS, charities have warned, as the health service missed one of its targets for the first time.

NHS guidelines say that when a GP makes an urgent referral for suspected cancer, 85 per cent of patients should wait no more than 62 days before receiving their first treatment.

Figures released yesterday show that this dropped from 85.8 per cent to 84.4 per cent for the three months from January to March, the first time that the target has been missed since it was introduced five years ago.

Mike Hobday, a director at Macmillan cancer Support, said: «This is the first breach of any cancer waiting time in England since 2009 and is a clear warning sign that the NHS ist under huge strain.»

Sean Duffy, national clinical director for cancer at NHS England, said: «It is vital cancer patients are diagnosed and treated quickly so they have the best possible chance of recovery.»

«Latest figures show nationally the NHS has met and exceeded seven out of eight cancer waiting-time standards. But there is variation in meeting the challenging standards, and national performance against one of the targets has dipped.»

Mr Hobday added: «It is of great concern that the number of trusts missing this target has doubled over the past year. Around one in four of the trusts that were hitting the target at the start of 2013-14 are now missing the target.»

The proportion of patients seen by a specialist within two weeks of an urgent GP referral has also dropped from 95,6 per cent to 95 per cent. ...

The Times, May 31, 2014

That's where the money is

How to hand over $272 billion a year to criminals

Medical science is hazy about many things, but doctors agree that if a patient is losing pints of blood all over the carpet, it is a good idea to stanch his wounds. The same is true of a health-care system. If crooks are bleeding it of vast quantities of cash, it is time to tighten the safeguards.

In America the scale of medical embezzlement is extraordinary. According to Donald Berwick, the ex-boss of Medicare and Medicaid (the public health schemes for the old and poor), America lost between $82 billion and $272 billion in 2011 to medical fraud and abuse. The higher figure is 10% of medical spending and a whopping 1.7% of GDP – as if robbers had made off with the entire output of Tennessee or nearly twice the budget of Britain's National Health Service (NHS).

Crooks love American health care for two reasons. First, as Willie Sutton said of banks, it's where the money is – no other country spends nearly as much on pills and procedures. Second, unlike a bank, it is barely guarded.

Some scams are simple. Patients claim benefits to which they are not entitled; suppliers charge Medicaid for non-existent services. One doctor was recently accused of fraudulently billing for 1,000 powered wheelchairs, for example. Fancier schemes involve syndicates of health workers and patients. Scammers scour nursing homes for old people willing, for a few hundred dollars, to let pharmacists supply their pills but bill Medicare for much costlier ones. Criminal gangs are switching from cocaine to prescription drugs – the rewards are as juicy, but with less risk of being shot or arrested. One clinic in New York allegedly wrote bogus prescriptions for more than 5m painkillers, which were then sold on the street for $30-90 each. Identity thieves have realised that medical records are more valuable than credit-card numbers. Steal a credit card and the victim quickly notices; photocopy a Medicare card and you can bill Uncle Sam for ages, undetected.

It is hard to make such a vast system secure: Medicare's contractors process 4.5m claims a day. But pointless complexity makes it even harder. Does Medicare really need 140,000 billing codes, as it will have next year, including ten for injuries that take place in mobile homes and nine for attacks by turtles? A toxic mix of incompetence and political gridlock has made matters worse. Medicare does not check new suppliers for links to firms that have previously been caught embezzling (though a new bill aims to fix this). Fraud experts have long begged the government to remove Social Security numbers from Medicare cards to deter identity thieves – to no avail.

Start by closing the safe door

One piece of the solution is obvious: crack down on the criminals. Obamacare, for all its flaws, includes some useful measures. Suppliers are better screened. And when Medicaid blackballs a dodgy provider, it now shares that information with Medicare – which previously it did not. For every dollar spent on probing health-care fraud, taxpayers recover eight. So the sleuths' budgets should be boosted, not squeezed, as now.

But the broader point is that American health care needs to be simplified. Whatever its defects, Britain's single-payer National Health Service is much simpler, much cheaper and relatively difficult to defraud. Doctors are paid to keep people well, not for every extra thing they do, so they don't make more money by recommending unnecessary tests and operations—let alone billing for non-existent ones.

Too socialist for America? Then simplify what is left, scale back the health tax-perks for the rich and give people health accounts so they watch the dollars that are spent on their treatment. After all, Dr Berwick's study found that administrative complexity and unnecessary treatment waste even more health dollars than fraud does. Perhaps that is the real crime.

Kommentar der Redaktion

Das interessante an der Studie ist vor allem, dass die administrative Komplexität die Hauptursache der finanziellen Verschwendung im Gesundheitswesen ist. Bezüglich Komplexität: Wir bewegen uns in der Schweiz immer mehr in dieselbe Richtung...
Werden wir auch die gleichen Folgen wie in USA bei uns erleben?

Pharma opens new front in war on cancer

The industry now has a chance to develop a generation of bockbuster drugs

It is the Holy Grail of medical science. Ever since Hippocrates, the Greek physician, first described the disease more than 2,000 years ago, generation after generation of doctors have searched in vain for a cure for cancer.

This history of failure instils oncologists with a natural sense of caution, which makes it all the more striking when some say their profession is on the cusp of the biggest breakthrough in cancer therapy for decades.

«I've been an oncologist for a long time and I've never experienced as much excitement,» says Edward Bradley, head of Oncology Innovative Medicines at Medimmune, part of AstraZeneca, the UK drugmaker. This excitement will come to a head in Chicago [May 30-June 3] as thousands of scientists gather for the annual meeting of the American Society of Clini-

cal Oncology. Taking centre stage are a series of experimental drugs that promise to open a new front in the war on cancer.

Whereas traditional treatments such as chemotherapy and radiotherapy have been likened to «carpet bombing», the new class of immunotherapy drugs are more akin to precision-guided missiles that hunt and destroy cancer cells. Their potential is stirring optimism not only among scientists and patients but also among investors eyeing a multibillion-dollar windfall for the four main companies behind the medicines: Merck & Co, Bristol-Myers Squibb, Roche and AstraZeneca.

Andrew Baum, an analyst at Citigroup, predicts that cancer immunotherapy will become the backbone of treatment for 60 per cent of cancers within 10 years, generating peak annual revenues of $35bn or more. This would exceed the value of past blockbuster drug categories such as cholesterol-busting statins and could go a long way towards reviving the fortunes of an industry struggling for growth.

Mr Baum has been championing the potential of immunotherapy since declaring in a report last year «the beginning of the end for cancer». Twelve months later, he says he is feeling even more bullish as fresh trial data emerge to support his belief that the new drugs will transform cancer into «something akin to a chronic disease».

Immunotherapy includes a range of techniques to harness the body's immune system to attack cancer. Scientists have been experimenting with the concept since 1850, when German physicians noticed that tumours would sometimes shrink when they became infected - stimulating an immune response. «It is not a new idea but we are finally seeing that it is going to work,» says Paul Higham, chief executive of Immatics, a German biotech company that has an immunotherapy partnership with Roche. «The question now is what is the best way to do it.»

The leader so far has been US-based Bristol-Myers Squibb, whose Yervoy treatment for advanced melanoma - the most deadly form of skin cancer - was the first product of its kind to reach market, with sales of almost $1bn last year. Without the drug, a patient with advanced melanoma would typically die within a year. When treated with Yervoy, 22 per cent were still alive three years later and 17 per cent survived for seven years.

Some of the next wave of drugs look still more promising. The focus at Asco will be on a category known as anti-PD-1s and anti-PD-L1s, which aim to remove the «invisibility cloak» that cancer cells use to roam the body unchecked.

Programmed death receptor 1s (PD1s) are proteins that act as a brake on the immune system to stop healthy cells from being attacked - but they are exploited by cancer cells to avoid detection. When this process is blocked, cancer cells suddenly find themselves exposed to the body's disease-busting killer T-cells.

«Tumours are damn smart,» Mr Baum says. «It's like Whack a Mole. As soon as you block one pathway they find another. But, with a little help, the immune system is the one thing smart enough to keep up.»

Bristol-Myers Squibb is again at the forefront with nivolumab, a drug that has kept 43 per cent of advanced melanoma patients alive for two years in trials. But it is facing stiff competition from US rival Merck - which has jumped ahead in the race for regulatory approval - as well as Roche of Switzerland and AstraZeneca, which are scrambling to catch up. Analysts think all four could secure regulatory approval by the end of next year.

Having previously shown promise in treating lung cancer as well as melanoma, data released at Asco is expected to demonstrate the drugs' potential to tackle several other forms of the disease, including cancers of the kidney, bladder, head and neck. Another focus will be on trials of combination therapies that twin the new drugs with other medicines in a bid to increase response rates.

«It is an oversimplification to see this as a horse race in which the winner is the first to market,» Mr Baum says. «Who ends up generating most economic value is going to be determined by a number of factors, including who has the right combinations.» This explains why Roche and AstraZeneca, which have broad portfolios of cancer drugs to mix and match, still feel they can be competitive even though they are currently trailing Bristol-Myers Squibb and Merck.

Novartis, another big oncology performer, is placing its bets on a different form of immunotherapy that involves removing patients' T-cells from their bodies and re-engineering them to destroy cancer cells once reinjected. In early trials, 19 of 22 children suffering from acute lymphoblastic leukaemia went into complete remission after treatment.

Inevitably, scientists warn there will be setbacks. There had been high hopes, for example, that nivolumab and Yervoy would provide Bristol-Myers Squibb with a powerful combination therapy. However, trial results this month showed that nearly half the 46 participants suffered bad side effects and there were three «treatment-related» deaths – raising doubts over whether the benefits outweighed the risks.

Pricing is likely to be another challenge. Annual global spending on cancer drugs more than doubled in the past decade to $91bn in 2013. The figure looks certain to rise further given that the World Health Organisation expects a 57 per cent increase in worldwide incidence of cancer in the next 20 years as western populations age and those in developing countries adopt less healthy lifestyles.

These trends should ensure strong demand for new cancer drugs but also put pressure on pricing as countries from the US to China battle to contain rising healthcare costs. Mr Baum thinks society will reward industry for coming up with new ways to treat a disease responsible for a quarter of all developed-world deaths. He highlights Bristol-Myers Squibb's success with Yervoy at a price of $120,000 a course. «These are not incremental drugs that add a couple of months' of extra life,» Mr Baum says. «They are potentially transformational.»

Financial Times, May 31, 2014

GSK in $350m oncology deal

Glaxo Smith-Kline has struck a deal potentially worth more than $350m to develop new cancer drugs with a UK biotech company, less than six weeks after agreeing to sell its existing oncology products to Novartis.

Under the agreement to be announced today, GSK will pay Adaptimmune as much as $350m over the next seven years, subject to development milestones being met. Further payments would be due in subsequent years if GSK exercises all its options and targets continue to be met. In addition, Adaptimmune would receive sales royalties on any products that reach market.

Working with the Oxford-based biotech, GSK will develop cell-based cancer therapies that involve re-engineering patients' white blood cells to improve the body's ability to fight tumours.

The deal shows that GSK has not given up on cancer despite its $16bn disposal in April. At the time of that deal, GSK said it did not have enough scale in the oncology market to compete effectively with its existing treatments for skin cancer, breast cancer and leukaemia.

However, Patrick Vallance, president of pharmaceutical research and development for GSK, said it would be wrong to interpret the Novartis deal as a full-scale retreat from oncology.

«We won't always be the best company to commercialise products but we will continue to focus on [oncology] R&D,» he said.

Once a new product was ready for market, GSK would decide whether it could generate most value by doing its own commercialisation or instead seeking a partner or buyer.

James Noble, Adaptimmune chief executive, said the privately owned company had a choice of five potential partners, including three other top 10 drugmakers, but chose GSK because it promised the most collaborative approach.

The transaction will put GSK back in the race for a new generation of oncology treatments that harness the body's immune system to hunt and destroy cancer cells.

Bristol-Myers Squibb, Merck & Co, Roche and AstraZeneca are leading the charge with a class of medicines called checkpoint inhibitors, which some analysts have likened to HIV drugs in their potential to extend life expectancy.

However, the Adaptimmune deal will put GSK alongside Novartis in pursuing an alternative form of immunotherapy that involves taking disease-fighting «T-cells» out of the body and modifying them. Once reinjected, the cells bind on to cancer cells and destroy them. Once reinjected, the cells bind on to cancer cells and destroy them.

Analysts have cautioned that the field is shaping up to be fiercely competitive.

Financial Times, June 2, 2014

Rethinking strategies for two cancers

Study cites advantages of early chemotherapy for treating prostate

Many men with prostate cancer put off using chemotherapy as long as possible, fearing its side effects.

But a new study has found that men given chemotherapy early in their treatment for advanced disease lived a median of nearly 14 months longer than those who did not get early chemotherapy. The result could upend the established treatment practice, researchers said here on Sunday.

«We haven't seen survival benefits like that for any therapy in prostate cancer,» said Dr. Michael J. Morris, an associate professor at the Memorial Sloan-Kettering Cancer Center, who was not involved in the study but was selected to publicly comment on it at the annual meeting of the American Society of Clinical Oncology.

Another study being presented Sunday found that drugs called aromatase inhibitors might be better than the standard drug tamoxifen in preventing a recurrence of disease in premenopausal women with early breast cancer.

Both studies were featured in the plenary session on Sunday, meaning they were deemed among the most noteworthy of the more than 5,000 studies being presented at the meeting.

Dr. Nicholas J. Vogelzang, an author of the study on prostate cancer, said the findings would change practice. The challenge, he said, is getting men to agree.

«Not many of them want to do chemotherapy, even though the numbers are convincing,» said Dr. Vogelzang, who works at the Comprehensive Cancer Centers of Nevada.

The study's findings apply to a fairly narrow group of patients – men whose cancer has already spread beyond the prostate gland at the time of diagnosis, or whose cancer has come back after surgery or radiation treatment and still remains susceptible to hormone therapy.

Only a small fraction of men have metastatic prostate cancer at the time of the initial diagnosis because prostate cancer screening using a blood test typically detects the disease before it has spread.

The study, sponsored by the National Cancer Institute, involved 790 men who received either only hormone therapy or hormone therapy in addition to at most six infusions of docetaxel spaced three weeks apart.

Those who received the chemotherapy lived a median of 57.6 months, compared with 44 months in the control group, a difference of 13.6 months. The difference in survival was even greater – 17 months – for the patients whose cancer had spread more extensively. Dr. Morris of Sloan-Kettering said those men were the best candidates for early chemotherapy.

Docetaxel is sold under the brand name Taxotere by Sanofi, but generic versions are available. It was approved for metastatic prostate cancer in 2004. In the last few years, several other drugs have been approved, like Zytiga from Johnson & Johnson and Xtandi from Medivation and Astellas Pharma.

But docetaxel and the newer drugs are typically used after hormone therapy has stopped working. In that setting, each of them has extended median survival by about two to five months in clinical trials.

Dr. Matthew R. Cooperberg, associate professor of urology at the University of California, San Francisco, said doctors were starting to use the newer agents before docetaxel, pushing chemotherapy further back in the sequence.

So the new study «is, to an extent, bucking the tide,» he said.

In breast cancer, women with estrogen-responsive disease typically take drugs for at least five years after their tumor has been removed surgically, to prevent cancer from recurring.

Aromatase inhibitors are generally considered a better choice than tamoxifen for postmenopausal women. But aromatase inhibitors work only when women have low estrogen levels, which usually rules them out for premenopausal women.

The new study – actually two studies being analyzed together to accumulate nearly 4,700 patients – involved suppressing the functioning of the ovaries so that the younger women could take an aromatase inhibitor.

Five years of an aromatase inhibitor in addition to ovarian suppression proved superior to five years of tamoxifen in addition to ovarian suppression. After five years, 91.1 percent of those who received the aromatase inhibitor, exemestane, were free of cancer, compared with 87.3 percent of those who received tamoxifen with ovarian suppression. (In the United States, tamoxifen is typically used without ovarian suppression.)

International New York Times, June 3, 2014

Bund verzögert Zugang zu lebensrettenden Medis

Schweizer Patienten müssen auf neue Medikamente warten, die anderswo längst von der Grundversicherung bezahlt werden. Der Grund: Das Bundesamt für Gesundheit hintertreibt die vom Bundesrat versprochene Beschleunigung.

Seit dem 1. Juni 2013 ist eine Verordnung des Bundesrates in Kraft, die das Bundesamt für Gesundheit (BAG) verpflichtet, in der Regel innert 60 Tagen nach der Zulassung eines neuen Medikaments durch die Arzneimittelbehörde Swissmedic zu entscheiden, ob das Arzneimittel von der Grundversicherung vergütet wird. Gesundheitsminister Alain Berset reagierte damit auf scharfe Kritik von Novartis und Roche. Sie hatten das BAG als «innovationsfeindlich» angeprangert, weil es im Schnitt 200 Tage für den Entscheid brauchte. Es schade damit sowohl den Patienten als auch der Pharmaindustrie.

Ein Jahr nach Inkrafttreten zeigt sich, dass die Verordnung toter Buchstabe geblieben ist. Bei mehr als der Hälfte der 37 neu zugelassenen Originalpräparate hat das BAG die 60-Ta-

ge-Frist zur Aufnahme in die Spezialitätenliste der Grundversicherung nicht eingehalten. In 13 Fällen hat es noch gar keinen Entscheid gefällt, obwohl die Frist schon längst überschritten ist.

Zum Beispiel beim Blutkrebsmedikament Folotyn: Es wurde von Swissmedic am 11. Oktober 2013 zugelassen. Ärzte dürfen es also seit 238 Tagen verschreiben. Aber die Grundversicherung bezahlt es nicht, weil das BAG seinen Entscheid hinauszögert. Für schwer kranke Patienten, die das Medikament nicht selber zahlen können, kann das fatale Folgen haben.

Besonders stossend ist, dass lebensrettende Medikamente in anderen Ländern längst von der Grundversicherung erstattet werden, während sich die Schweizer Patienten gedulden müssen. Beispielsweise beim Blutkrebsmittel Jakavi von Novartis. Es wurde in der Europäischen Union am 23. August 2012 zugelassen. In Deutschland, Österreich, Grossbritannien und Dänemark erfolgte die Erstattung innerhalb von zwei Monaten nach der Zulassung. Die Schweiz hinkte Europa klar hinterher: Am 27. Dezember 2012 wurde Jakavi von Swissmedic zugelassen. Geschlagene 370 Tage später, am 1. Januar 2014, nahm es das BAG in die Spezialitätenliste der Grundversicherung auf.

Die Pharmaindustrie kritisiert das Bundesamt für Gesundheit scharf. «Der Wille, die Beschleunigung umzusetzen, fehlt bei den zuständigen Beamten im BAG», sagt Sara Käch, Sprecherin des Branchenverbandes Interpharma. «Die von Bundesrat Berset versprochene, seit einem Jahr in der Verordnung vorgeschriebene Beschleunigung hat nichts bewirkt. Die Verordnung wird in der Praxis nicht umgesetzt.» Interpharma hat deshalb kürzlich bei Bundesrat Alain Berset und BAG-Chef Pascal Strupler interveniert und sie aufgefordert, bei ihren Untergegebenen einzuschreiten.

Das BAG sieht jedoch kein Problem und sagt, es habe die 60-Tage-Frist in 80 Prozent der Fälle eingehalten. «Das BAG setzt die Verordnung mehrheitlich innerhalb der vorgegebenen Zeit um», sagt Sprecher Daniel Dauwalder. Zu diesem Ergebnis kommt das Bundesamt allerdings nur, weil es entgegen der Verordnung nach eigenen Arbeits- und nicht nach Kalendertagen rechnet. Zudem hat es alle Gesuche aus dem Jahr 2014 und alle hängigen Gesuche, die tendenziell besonders lange dauern, herausgerechnet, um auf das gewünschte Ergebnis zu kommen.

Interpharma wirft dem BAG vor, es verschulde die Zeitverzögerung, indem es den Preis unter jenen der sechs Vergleichsländer drücke. Das löse lange Preisverhandlungen aus. «Innovative Medikamente werden in der Schweiz systematisch unter dem europäischen Auslandpreis eingestuft», sagt Manfred Heinzer, der Leiter von Roche Pharma Schweiz. «Diese für uns nicht akzeptablen Preisvorstellungen führen zu Verzögerungen im Zugang zu hoch innovativen, neuen Produkten, welche von den Patienten dringend benötigt werden.» Beispielsweise habe das BAG beim Brustkrebsmedikament Kadcyla über einen langen Zeitraum an einem Preis festgehalten, der rund 30 Prozent tiefer als derjenige in Deutschland, Frankreich und weiteren Referenzländern gelegen wäre.

Dabei kosten neue Medikamente in der Schweiz schon heute weniger als in den sechs Vergleichsländern. Im Schnitt sind sie 13 Prozent billiger, wie ein von Interpharma durchgeführter Preisvergleich bei den seit 2011 kassenpflichtigen Medikamenten mit neuen Wirkstoffen zeigt. Noch grösser ist der Preisunterschied bei jenen Medikamenten, wo der Zusatznutzen nach den strengen deutschen Regeln klar belegt ist. Hier liegt er bei 15 Prozent. Gegenüber Deutschland sind es sogar 29 Prozent.

«Diese Praxis des BAG führt zu einem innovationsfeindlichen Umfeld in der Schweiz», sagt Interpharma-Sprecherin Sara Käch. «Und dies ausgerechnet in dem Land, das über Investitionen in Forschung und Entwicklung, Arbeitsplätze und Exporte wie kein anderes weltweit von der Pharmaindustrie profitiert. Das ist ein schlechtes Signal gegenüber den hier ansässigen Firmen.» Zudem widerspreche es dem Willen des Parlaments. Dieses hatte vor einem Jahr verlangt, dass bei der Preisfestsetzung die Innovation berücksichtigt wird.

Schweiz am Sonntag, 8. Juni 2014

Die vergessenen Asbestopfer

Das Urteil des Gerichtshofs für Menschenrechte im März 2014 war für Asbestgeschädigte eine grosse Genugtuung. Endlich hat ein Gericht gesagt, dass es nicht in Ordnung ist, wenn Ansprüche auf Schadenersatz verjähren, bevor die Betroffenen vom Schaden wissen. Doch die Freude währte nur kurz. Einen Monat später hat das Bundesgericht eine weitere pendente Asbestklage sistiert, und zwar bis die eidgenössischen Räte die Verjährungsrechtsrevision abschliessen.

Das Gericht will dem gesetzgeberischen Prozess nicht vorgreifen und keine Präjudizien schaffen, die dem künftigen Recht widersprechen könnten. Dabei missachtet das Bundesgericht aber die Tatsache, dass schon das heutige Obligationenrecht bei einem Teil der Klagen eine geschädigtenfreundlichere Rechtsprechung zuliesse – dann nämlich, wenn der Geschädigte bei der Asbestverarbeiterin angestellt war. Weniger Spielraum haben die Gerichte, wenn es keinen Vertrag gab und der Betroffene beispielsweise als Anwohner geschädigt wurde.

Ungeachtet dieser möglichen Differenzierung weist das Bundesgericht seit 1980 alle Asbestklagen als verjährt ab. Immerhin betrifft die Sistierung einen sogenannten ausservertraglichen Fall. Für die andern Fälle, zu denen auch der im März in Strassburg beurteilte gehört, besteht also Hoffnung auf eine Behandlung.

So oder so schafft das Bundesgericht eine weitere Unsicherheit für Rechtsuchende. Sie müssen möglicherweise warten, bis das Parlament die Gesetzesrevision zu Ende beraten hat, was noch Jahre dauern wird. Im schlimmsten und gleichzeitig wahrscheinlichsten Fall resultieren daraus keine substanziellen Verbesserungen für Opfer von Langzeitschäden. Darauf deutet das Gezerre um die künftige Verjährungsfrist hin, die schon begonnen hat: Die Wirtschaft wehrt sich gegen die geplante Verlängerung von 10 auf 30 Jahre; Opfervertretern hingegen genügen 30 Jahre nicht.

Abgesehen davon vergisst die Politik Tausende Asbestopfer: Bereits verjährte Fälle bleiben es voraussichtlich auch mit einem neuen Gesetz – und sie machen den grössten Teil der mehreren Tausend Betroffenen aus. Es ist ein Fehler von Justizministerin Simonetta Sommaruga, einen runden Tisch zur Klärung der Asbestfrage abzulehnen. Der Bund sollte parallel zur Gesetzesrevision einen Entschädigungsfonds für die vergessenen Fälle initiieren. So würde das Leid der Betroffenen gelindert, wodurch die juristische Aufarbeitung an Bedeutung verlieren würde.

Tages-Anzeiger, 11. Juni 2014

Alain Berset will Medikamentenpreise nochmals deutlich senken

Die Vorstellungen des SP-Bundesrats dürften in der Pharmaindustrie auf heftigen Widerstand stossen. Betroffen sind auch die Hersteller von Generika

Noch bevor die letzte Preissenkungsrunde abgeschlossen ist, steht bereits die nächste ins Haus. Gesundheitsminister Alain Berset wird in Kürze einen Entwurf vorlegen, wie die Medikamentenpreise in der Schweiz neu festgelegt werden sollen. Die Vorstellungen des SP-Bundesrats dürften der Pharmaindustrie missfallen, da sie bereits bei der laufenden Runde zwischen 2012 und 2015 Einbussen von über 700 Millionen Franken hinnehmen muss. Laut Informationen des TA will Berset zusätzlich folgende Änderungen vornehmen:

Auslandpreisvergleich: Bisher werden die hiesigen Preise mit jenen von Deutschland, den Niederlanden, Frankreich, Österreich, Dänemark und Grossbritannien verglichen. Nun sollen bis zu drei weitere Länder hinzukommen. Es ist davon

auszugehen, dass dies Nationen mit tieferen Medikamentenpreisen sein werden, was sich kostendämpfend auf die Schweiz auswirken würde.

Toleranzmarge: Bei der laufenden Runde kam der Bundesrat der Pharmaindustrie entgegen, indem er die Umrechnung der ausländischen Preise in Franken mit einer Marge von 5 Prozent abfederte. So wurde den Herstellern ein Wechselkurs von 1.29 Franken pro Euro zugestanden, obwohl der vom Bundesamt für Gesundheit (BAG) festgelegte Durchschnittskurs 1.23 Franken beträgt. Nun soll diese Toleranzmarge von 5 auf 3 Prozent gesenkt werden.

Nutzen eines Medikaments: In der letzten Preissenkungsrunde wurde fast ausschliesslich auf die ausländischen Preise abgestellt. Nun soll wie früher wieder der Nutzen des Medikaments im Vergleich zu ähnlichen Präparaten einbezogen werden. Allerdings soll der Auslandpreisvergleich ein höheres Gewicht erhalten.

Kurzfristige Kehrtwende

Diese und andere Änderungen kann Berset über die entsprechende Verordnung regeln. Die Vernehmlassung soll dem Vernehmen nach innert 30 Tagen durchgeführt werden. Es ist gut möglich, dass einige Details noch geändert werden, die Richtung ist jedoch eindeutig.

Innerhalb der Pharmaindustrie zeigen sich diverse Vertreter denn auch irritiert und fürchten sich vor einem weiteren markanten Einschnitt. Viel von dem, was an den runden Tischen mit dem BAG in den letzten Monaten besprochen wurde, sei nicht mehr übrig. Der Widerstand der Pharmabranche wird heftig ausfallen. Bevor der Entwurf nicht vorliegt, will sich jedoch niemand offiziell dazu äussern. Laut Beobachtern habe vieles auf einen Kompromiss hingedeutet, mit der die Pharmaindustrie hätte leben können. Der Kurswechsel Bersets sei offenbar relativ kurzfristig erfolgt.

Eine Änderung fasst der Gesundheitsminister auch bei den Generika ins Auge. Berset favorisiert das von Preisüberwacher Stefan Meierhans vorgeschlagene Festbetragssystem. Dabei müssen die Patienten den Aufpreis gegenüber dem billigsten Generikum selber berappen. Beim bisherigen Mechanismus müssen Nachahmerpräparate eine bestimmte Preisdifferenz zum Originalmedikament aufweisen. Laut Meierhans könnten mit dem Systemwechsel jährlich 380 Millionen Franken gespart werden. Die Generikaindustrie fürchtet happige Einbussen und sieht die Wahlfreiheit der Patienten in Gefahr. Für eine solch weitgehende Anpassung muss das Gesetz geändert werden. Damit liegt die Hürde höher als bei den Preissenkungen der Originalpräparate, da das Parlament darüber befinden muss.

Tages-Anzeiger, 11. Juni 2014

Ein Boykott verletzt den Forschergeist

Diesen Erfolg kann dem Hirnforscher Henry Markram keiner mehr nehmen: Das Human Brain Project ist wohl das seit Jahrzehnten umstrittenste Forschungsprojekt der Schweiz. Es hat somit die Neuroforschung auf die Landkarte der öffentlichen Aufmerksamkeit gesetzt.

Was bisher geschah: Der schillernde, dandyhafte südafrikanisch-israelisch-schweizerische Neuroforscher war 2002 mit einer Vision an die ETH Lausanne gekommen: Wenn es gelingt, alles Wissen über das Gehirn in einen vernünftigen Computer einzuspeisen, wird man dieses dereinst simulieren können. Und dann werde uns wie Schuppen von den Augen fallen, was das Gehirn ausmacht und wie es funktioniert. Aber nicht nur das: Weil ein solcher Super-Supercomputer erst noch gebaut werden muss, werden auf dem Weg dahin reichlich neue Einsichten fruchten, vor allem auch im Bereich der Informationstechnologie.

Eine derart allumfassende Vision braucht natürlich, das war Markram von Beginn weg klar, eine den Rahmen sprengende Finanzierung. Aus neu geschaffenen EU-Töpfen, die er selber vorgeschlagen hat, hat er prompt den Zuschlag für rund eine Milliarde Euro für einen Zeitraum von zehn Jahren erhalten. Das Human Brain Project wurde im Januar 2013 gegen harte Konkurrenz zum EU-Flaggschiff-Projekt erklärt. Im vergangenen Oktober dann startete die erste rund dreijährige Phase des Projektes mit rund 200 Forschern aus 112 Institutionen.

Doch nun haben rund 150 Neurowissenschaftler aus ganz Europa einen offenen Brief an die EU-Kommission veröffentlicht, in dem sie die wissenschaftlichen Ziele und auch die Führung des Megaprojektes hart kritisieren. Das Projekt sei zu computerlastig und die Vergabe von Unterprojekten zu wenig transparent. Internationale Standards würden nicht eingehalten. Anlass ist eine Eingabe der dreiköpfigen Führungscrew um Henry Markram an die EU-Kommission, in der für die zweite Phase ein Unterprojekt über die kognitive Neuroforschung aus dem Kernprojekt gestrichen wurde. Die Initianten des Briefes kommen aus den Reihen dieser kognitiven Neuroforscher und fordern von der EU-Kommission eine minutiöse und peinlich genaue Prüfung des ganzen Projektes, bevor die Gelder der zweiten Phase bewilligt würden, für die ab 2016 rund 100 Millionen Euro pro Jahr vorgesehen sind. Andernfalls rufen die Unterzeichnenden dazu auf, fortan auf eine Beteiligung am Projekt zu verzichten – die Forscher sollen das Human Brain Project also boykottieren.

Guruhafte Art

Erstaunlich ist der grosse Anklang, den der Protestbrief gefunden hat. Bis gestern Nachmittag waren es bereits mehr als 500 Wissenschaftler, darunter bekannte Namen wie der Zürcher Neuroökonom Ernst Fehr oder die Philosophin Ursula Pia Jauch. Viele davon sind nicht direkt in das Vorhaben involviert, sondern wurden von einem generellen Unbehagen gegenüber dem Megaprojekt motiviert – aber auch die guruhafte Art von Projektleiter Markram ist umstritten.

Die wissenschaftliche Kritik ist nicht neu: Einige Neuroforscher haben von Beginn weg bezweifelt, dass allein aus der massiven Anhäufung von Daten die realen Abläufe im Gehirn verständlich würden und so Wege für die Behandlung von Krankheiten wie Alzheimer, Depression zu finden seien. Nicht weniger als das steht auf dem Banner des Human Brain Project. Markram und seine Leute wollen sich jedoch nicht daran messen lassen und antworten, dass es eigentlich um Forschung im Bereich der Informationstechnologie handle, welche die Neuroforschung als Ganzes voranbringe.

Die Auseinandersetzung hat mittlerweile Charakterzüge eines Glaubenskrieges angenommen: Jeder glaubt, sich sofort und laut dazu äussern zu müssen. Die Forderung, das Management kritisch, genau und unabhängig zu überprüfen, ist sicher richtig. Der Boykott-Aufruf jedoch widerspricht dem Geist der freien Forschung zutiefst, die vom freien Gedankenaustausch und dem ständigen Streit der Ideen lebt. Dies auch im Interesse des gemeinsamen Ziels, nämlich dem Verständnis des so wundersam komplexen Gehirns.

Tages-Anzeiger, 11. Juli 2014

Joint Venture zwischen der Pharma und Hasch-Gegnern

US-Pharmakonzerne finanzieren die Gegner der Cannabis-Liberalisierung. Sie befürchten, dass ihre opiathaltigen Schmerzmittel vom Markt verdrängt werden.

Polizeigewerkschaften, Gefängnisunternehmen, Bierbrauer und Familienverbände haben im Kampf gegen die Cannabisfreigabe in den USA einen finanzkräftigen Verbündeten gefunden: Auch etliche Hersteller von starken opiathaltigen Schmerzmitteln widersetzen sich der Liberalisierung oder fordern rigide Regeln für den privaten Konsum. Der ist seit dieser Woche auch im Bundesstaat Washington problemlos möglich: Nach Colorado hat der Staat im Nordwesten der USA den Verkauf von Cannabis ebenfalls legalisiert.

Angeführt wird die Opposition von Patrick Kennedy, Sohn des verstorbenen Senators Ted

Kennedy. Patrick Kennedy litt an Alkohol- und Drogenproblemen und setzte 2006 seinen Ford Mustang in die Sicherheitsschranken vor dem Capitol in der US-Hauptstadt Washington. Er gab zu, ein rezeptpflichtiges Schmerzmittel mit opiathaltigen Wirkstoffen konsumiert zu haben.

Heute ist der 46-Jährige wieder suchtfrei. 2013 gründete er die Bewegung Smart Approaches to Marijuana (SAM) als Antwort auf den Entscheid der Stimmbürger in Colorado und Washington, den Handel und Konsum mit Cannabisprodukten freizugeben.

Eine tödliche Suchtwelle

SAM und anderen Oppositionsgruppen geht es nicht allein um Aufklärung von Jugendlichen. Ein vertrauliches Dokument der Partnership for Drug-Free Kids zeigt, dass mehrere Pharmafirmen die Kampagnen gegen die Haschfreigabe mitfinanzieren. Das Magazin «The Nation» berichtet gestützt auf das Dokument, dass Purdue Pharma und Abbott Laboratories zu den grössten Spendern der Partnership gehören. Bekannt ist auch, dass Pharmafirmen und Polizeigewerkschaften in Kalifornien bis zur Hälfte der Spenden an Anti-Hasch-Abstimmungskomitees beisteuerten.

Purdue zählt zusammen mit der Pharmafirma Alkermes auch zu den Geldgebern der Community Anti-Drug Coalition of America (CADCA). Weitere Financiers der Anti-Hasch-Bewegung sind gemäss «The Nation» Pfizer sowie die Johnson-&-Johnson-Tochter Janssen.

All diesen Unternehmen ist gemeinsam, dass sie starke Schmerzmittel herstellen, die aus Opium gewonnen werden oder synthetisches Opium enthalten. Die Präparate sind entsprechend suchtgefährlich. Patrick Kennedy selber hatte das Purdue-Präparat Oxycontin geschnupft, als er den Autounfall in Washington verursachte. Alkermes sorgte dieses Frühjahr für einen stürmischen Protest, als es das angeblich zehnmal stärkere Schmerzmittel Zohydro auf den Markt warf.

Diese Opiate in Form von Schmerzmitteln sind in den USA für eine enorme Suchtwelle verantwortlich. Die staatlichen Center for Disease Control und Prevention sind höchst besorgt: Jährlich sterben über 16'000 Abhängige an einer Überdosis solcher Schmerzmittel. Das sind mehr Menschen, als jedes Jahr wegen Heroin und Kokain den Tod finden. Zwar versuchen die Hersteller, den Missbrauch zu verhindern, indem sie die Pillen mit einer Schutzschicht versehen, die es unmöglich machen soll, sie zu einem schnupftauglichen Pulver zu zerreiben. Doch insbesondere in den ärmlichen Regionen des Südens ist die Oxycontin-Suchtwelle akut.

Für die Hersteller sind die Schmerzmittel ein grosses Geschäft. Purdue machte seit 1996 mehr als 27 Milliarden Umsatz mit Oxycontin. Im Strassenhandel erzielen opiathaltige Präparate Höchstpreise. Diese Woche wurde der Chefapotheker eines New Yorker Spitals des Drogenhandels angeklagt, weil er 200'000 Oxycontin-Pillen mit einem Schwarzmarktwert von 5,6 Millionen Dollar entwendet hatte.

Cannabis ist ein Schmerzmittel

Von der Schmerzmittelgefahr ist in den Aufklärungsbroschüren der Anti-Marihuana-Gruppen wenig zu sehen. In ihren Kampagnen richten sie sich einzig gegen die Freigabe und fordern stark einschränkende Konsumvorschriften. Dies, obwohl Marihuana für Chronischkranke als Alternative zu den Opiat-Schmerzmitteln verschrieben wird. Es sei heuchlerisch, sich nicht zu den Risiken der suchterzeugenden Schmerzmittel zu äussern und dabei Marihuana auf der Liste der gefährlichsten Drogen behalten zu wollen, kritisieren Ärztegruppen wie die Physicians for Responsible Opioid Prescribing. Es stelle sich somit die Frage, ob diese Gruppen von ihren Geldgebern aus der Pharmabranche beeinflusst würden.

Eine Antwort lässt sich vom Widerstand gegen die Zulassung des Schmerzmittels Zohydro ableiten. 42 Drogenaufklärungsgruppen unterschrieben im Frühjahr den Protestbrief an die Zulassungsbehörde. Doch die Partnership for Drug-Free Kids und die Anti Drug Coalition (CADCA) fehlten auf der Liste der Unterzeichner.

Tages-Anzeiger, 11. Juli 2014

Vor der Operation zum Gentest

Die Klinik Hirslanden bietet neu genetische Abklärungen an, um unerwünschten Medikamentenwirkungen vorzubeugen. Am Unispital Zürich wird die Methode bisher nur zurückhaltend eingesetzt.

Noch ist es erst eine Praxis, doch diese soll sich mit der Zeit zu einem Zentrum entwickeln. So, wie es in der Vergangenheit an der Klinik Hirslanden mit vielen Fachgebieten passiert ist: Ein Spezialist fängt an, und um ihn gruppieren sich immer mehr Kollegen. Die «personalisierte Medizin», die jetzt neu angeboten wird, ist für Klinikdirektor Daniel Liedtke eine «wichtige Innovation». Dabei geht es grob gesagt darum, dank Gentests Medikamente so einzusetzen, dass sie bestmöglich wirken beziehungsweise keine unerwünschte Wirkung haben.

Die Idee für das neue Angebot stammt von Thomas Szucs, hauptberuflich Direktor des Europäischen Zentrums für Pharmazeutische Medizin an der Universität Basel. Szucs' Karriere ist vielfältig. Er ist ausserordentlicher Professor, hat zwei Facharzttitel (Pharmazeutische Medizin und Präventivmedizin) und je einen Master in Public Health, in Unternehmensführung und in internationalem Wirtschaftsrecht. Er arbeitete an diversen Kliniken im In- und Ausland als Arzt, Ökonom oder Manager, war in der Pharmaindustrie tätig, und aktuell präsidiert er auch noch den Verwaltungsrat der Krankenversicherung Helsana. Wie kommt dieser «Hansdampf in allen Gassen», wie er in der Gesundheitsszene genannt wird, dazu, eine Praxis an einer Zürcher Privatklinik zu eröffnen? ...

...

Der Test inklusive Beratung kostet 950 Franken und wird von der Krankenkasse nicht übernommen. Klinikdirektor Liedtke erwartet vorerst keinen Ansturm. Aus seiner Sicht ist die Untersuchung vor allem für mehrfach kranke Personen sinnvoll: «Bei Risikopatienten kann ein gutes Arzneimittelmanagement über Erfolg oder Misserfolg einer Operation entscheiden.»

Am Universitätsspital Zürich wird die Pharmakogenetik bisher nur gezielt dort eingesetzt, wo ein Nutzen in Studien gezeigt werden konnte, wie Oberärztin Natascia Corti erklärt. Die Forschung habe erst bei wenigen Genen einen klaren Zusammenhang mit der Wirkung oder Nebenwirkung bestimmter Medikamente nachweisen können. Gentests ohne konkrete Problemstellung zu machen, hält die klinische Pharmakologin für verfrüht. Hingegen seien sie sinnvoll, wenn ein Problem vorliegt. «Wenn zum Beispiel ein Patient eine Unverträglichkeit mit einem Medikament aufweist, wird er zu uns geschickt. Wir klären dann ab und ordnen möglicherweise einen Gentest an.» Sehr wichtig sei danach, dass ein Spezialist die Testresultate bewertet und sie dem Patienten erklärt, damit dieser nicht beunruhigt ist. «Dafür braucht es pharmakologisches Wissen auf dem neusten Stand und eine entsprechende klinische Erfahrung.» ...

Tages-Anzeiger, 25. Juli 2014

Kommentar der Redaktion

In einem Expertenbericht, den das schweizerische Zentrum für Technologiefolgen-Abschätzung TA-Swiss im März dieses Jahres erstellt hat, warnen die Fachleute vor einer unkontrollierten breiten Anwendung. Viele Ergebnisse sind zudem alles andere als eindeutig. Nach zehn Jahren intensiver Genomforschung ist vor allem klar geworden, dass die Beziehung zwischen dem Erbgut und einer Krankheit äusserst komplex ist.

Philip Morris versus Uruguay

In den Fängen der Schattenjustiz

Der Tabakmulti Philip Morris mit Sitz in der Schweiz verklagt den Staat Uruguay wegen Gesundheitsvorschriften. Der Bund will nicht intervenieren.

Am 5. und 6. Februar 2013 fand hinter den verschlossenen Türen der Internationalen Handelskammer in Paris ein Treffen hochrangiger Wirtschaftsanwälte statt. Der italienische Richter Piero Bernardini und seine Kollegen Gary Born aus den USA und James Crawford aus Australien hatten knapp zwei Dutzend AnwältInnen, Regierungsvertreter und KonzernmanagerInnen zu einer Anhörung geladen.

Was an diesem Treffen gesagt wurde, blieb unter Verschluss. Kein Reporter war anwesend, keine Medienmitteilung wurde verschickt. Die Öffentlichkeit war ausgeschlossen. Dabei verhandelten die 26 anwesenden Herren und Damen während zweier Tage nichts weniger als die Souveranität eines Staates.

Der Fall trägt das Aktenzeichen ARB/10/7. Es geht um eine Klage von Philip Morris gegen die Republik Uruguay. Der Tabakkonzern beschäftigt weltweit über 87000 Angestellte, seit 2003 befindet sich seine Betriebszentrale in Lausanne. Viel ist nicht über das Verfahren bekannt, denn die Klage wird nicht vor einem ordentlichen Gericht in Uruguay, in der Schweiz oder in den USA verhandelt, sondern an einem fast unbekannten Schiedsgericht bei der Weltbank in Washington, dem ICSID, dem Internationalen Zentrum zur Beilegung von Investitionsstreitigkeiten.

Postkoloniales Vermächtnis

Diese Geschichte nahm ihren Anfang im März 2006, als Uruguay unter Präsident Tabaré Vasquez, einem Onkologen, das Rauchen in geschlossenen Räumen untersagte. Es war der erste Schritt der uruguayischen Regierung im Kampf gegen die Nikotinsucht, an der weltweit jedes Jahr über fünf Millionen Menschen sterben.

2008 und 2009 folgten weitere Gesetze: Zigarettenpackungen müssen seither beidseitig zu achtzig Prozent mit Hinweisen und Piktogrammen versehen werden, die vor den Gefahren des Rauchens warnen, und die Verkaufsstellen dürfen von jeder Marke jeweils nur eine Variante anbieten (zum Beispiel nur Marlboro Rot, nicht aber zusätzlich Marlboro Gold).

Die Tabakindustrie sieht dadurch ihr Geschäft gefährdet. Der Konzern Philipp Morris liess 2010 verlauten, dass er wegen der «extremen und uneffektiven Regulierungen» sieben von zwölf Markenvariationen vom uruguayischen Markt nehmen musste, unter anderem auch Marlboro-Varianten, die vierzig Prozent der Marlboro-Verkäufe ausmachten. Da der Tabakkrieg seine Investitionen bedroht sah, reichte er am Schiedsgericht des ICSID Klage gegen den Staat Uruguay ein. Lange wurde über die Höhe der Klagesumme spekuliert, der Konzern aber schwieg eisern dazu. Anfang Mai allerdings sah sich Philipp Morris genötigt, einen Beitrag der «Financial Times» zu korrigieren, die die Summe von zwei Milliarden US-Dollar genannt hatte. Seither ist klar: Es geht um 25 Millionen Dollar, wie Philipp Morris auf Anfrage bestätigt.

Die rechtliche Grundlage für die Klage am ICSID geht zurück auf ein sogenanntes Investitionsschutzabkommen, das die Schweiz 1991 mit Uruguay abschloss. Das Abkommen wurde zum Schutz von Auslandsinvestitionen geschaffen. Weltweit bestehen über 3000 solcher bilateraler und multilateraler Abkommen. Die Schweiz hat insgesamt 130 Abkommen unterzeichnet, den Grossteil mit Entwicklungsländern. ...
...

Das Hauptproblem bei diesem System der Investitionsabkommen liegt jedoch in dessen Gerichtsbarkeit. Über die Streitigkeiten befindet ein höchst intransparentes Schiedsgericht in Washington. Bei jedem Fall werden drei handverlesene Wirtschaftsanwälte zu Schiedsrichtern ernannt, je einer vom Kläger und vom Beklagten, und der Präsident von den beiden ernannten Richtern. Zu 96 Prozent sind diese Richter Männer, wie «Le Monde diplomatique» in seiner Juniausgabe berechnete. Ihre Stundenansätze betragen zwischen 300 und 650 Franken, wobei die Verfahren pro Richter 500 Stunden und mehr in Anspruch nehmen. Ist ein Urteil gefällt, kann dagegen keine Berufung eingelegt werden. Die Entscheide sind endgültig. ...
...

Bis zum Urteil dürfte noch ein weiteres Jahr vergehen. Eine Niederlage Uruguays könnte ein «entscheidender Schlag gegen die Weltgesundheitsorganisation WHO und die Länder des Südens in ihrem Kampf gegen die Folgen des Tabakmissbrauchs» sein, befürchtet Alliance Sud. Letzte Woche forderte sie deshalb die Schweiz zum Handeln auf. In einer diplomatischen Note, einer sogenannten Auslegungsnote, soll sich die Schweiz für Uruguay einsetzen. Das Land verfolgte schliesslich eine Antitabakgesundheitspolitik, die in Einklang mit den Empfehlungen der WHO stehe.

Beim zuständigen Staatssekretariat für Wirtschaft (Seco) will man davon nichts wissen. Die Schweiz sei nicht Partei. Zudem sei es nach den Regeln des ICSID gehalten, «nicht in das rechtshängige Verfahren einzugreifen».

WOZ, 17. Juli 2014

Kommentar der Redaktion

Wir verweisen auf drei vorausgegangene Artikel im Schweizer Krebsbulletin:
1/2011: 42-44, 2/2012: 124-125,
1/2014: 28-29.

Im ersten Artikel hatte Sergio Ferrari den früheren (und wahrscheinlich auch nächsten: die Präsidentenwahl erfolgt im Oktober 2014) Präsidenten von Urugay, Dr. Tabaré Vasquez, einen bekannten Onkologen, interviewt.

Seit langem und trotz einiger Anfragen im Parlament versucht die Schweizer Regierung, sich aus der Affäre zu ziehen, indem sie sagt, «es ist nicht our business». Das Problem ist eher, dass auch unsere Regierung vor Philipp Morris kuscht.

In der Tat hat die Schweiz auch die Framework Convention on Tobacco Control (FCTC) unterschrieben und ratifiziert. Das ist ein internationaler Vertrag, an den die Schweiz gebunden ist. Und was Uruguay getan hat, ist nur die Klauseln dieses internationalen Vertrages in die Praxis umzusetzen. Wahrscheinlich müssten die KLS und im Grunde genommen auch die anderen onkologischen Vereine in der Schweiz Druck auf unseren Bundesrat ausüben. Der Kampf gegen die Tabakmultis kann nicht nur ein Lippenbekenntnis bleiben.

Stellungnahme zum Leserbrief von M. Fey im Schweizer Krebsbulletin Nr. 2/2014, S. 101

Audiatur et altera pars

Jürg Nadig, Präsident SGMO

In seinem Leserbrief[1] kommentiert Marin Fey meinem Artikel zu Choosing wisely[2] im Schweizer Krebsbulletin vom März 2014.

Martin Feys Annahme, ich hätte mich ohne Rücksprache mit dem Vorstand oder den SGMO Mitgliedern im Namen der Fachgesellschaft gegen die Screening-Mammographie ausgesprochen und den Verzicht auf diese Leistung mit politischer Weisheit gleichgesetzt, kann nicht unwidersprochen bleiben. Liesse sich zeigen, dass M. Feys Annahme falsch ist, wäre es auch seine Schlussfolgerung.

Der Artikel gibt meine Grussadresse zur Eröffnung des DGHO Kongresses in Wien 2013 wieder. Ich beleuchtete Möglichkeiten und Grenzen von Choosing wisely. Eine solche Orientierung braucht keine Zustimmung des Vorstandes. Ich fragte nach der politischen Umsetzbarkeit solcher Empfehlungen am Beispiel der Mammographie: Könnte die Screening-Mammographie überhaupt aus dem Pflichtleistungskatalog gestrichen werden, wenn im Rahmen von Choosing wisely die Datenlage ergäbe, dass der Schaden den Nutzen überwiegt? Auf Grund früherer Erfahrungen sind Zweifel an der politischen Umsetzbarkeit evidenzbasierter Entscheide berechtigt: Die Versuche, in der Schwangerschaft die Ultraschall-Untersuchungen von drei auf zwei zu reduzieren löste in der Bevölkerung einen konzertierten medialen Entrüstungssturm aus. Die Verordnung wurde deshalb wieder aufgehoben. Andererseits wurde der Anspruch auf alternativmedizinische Leistungen zu Lasten der Sozialversicherung mit einer Volksinitiative in der Verfassung verankert, ohne dass für einzelne Methoden die Evidenz nachgewiesen wurde.

Mein Artikel erschien, als der Medical Board-Entscheid zum Mammographie-Screening diskutiert wurde. Ich hatte den Artikel der Redaktion des Krebsbulletins aber eingereicht, bevor der Medical Board Entscheid vorlag. Allein schon auf Grund der zeitlichen Verhältnisse kann mein Artikel also gar keine Stellungnahme zum Medical Board Entscheid sein. M. Feys Annahme trifft also nicht zu. Ein Kommentar zu seinen Schlussfolgerungen erübrigt sich damit.

Ich schrieb, Weisheit leuchte erst in der Retrospektive nach umfassender Würdigung aller Umstände auf. Entscheide am Krankenbett oder in der Sprechstunde müssten aber prospektiv hier und jetzt und naturgemäss ohne Kenntnis aller Umstände gefällt werden. Das ist eine tägliche Erfahrung. Sie illustriert eine gewisse Widersprüchlichkeit des Begriffes «Choosing wisely«. Da mich M. Fey in diesem Zusammenhang aber falsch zitiert, erübrigt sich auch hier ein Kommentar.

Einen Kommentar verlangt aber die Art und Weise seiner Konfliktaustragung: Interessenskonflikte unter den Onkologen sollten primär innerhalb der Fachgesellschaft einvernehmlich gelöst werden. Die dazu notwendigen Organe wären vorhanden. Wer sich aber aus der Fachgesellschaft verabschiedet, verbaut sich diese Möglichkeit und sucht den Weg an die Öffentlichkeit.

Hätte mir die Redaktion des Krebsbulletins vor dessen Publikation M. Fey's Artikel zur Stellung vorgelegt, hätte sich rasch gezeigt, dass er auf falschen Annahmen und Zitaten beruht. Eine Veröffentlichung hätte sich damit erübrigt. Nun haben die Mitglieder der SGMO erst retrospektive, dafür aber in Würdigung aller Umstände, die Möglichkeit, sich eine Meinung zu bilden, «whether they have chosen their chairman wisely».

Audiatur et altera pars: Gehört werde auch der andere Teil.

1. Fey M. Kommentar zum Artikel in der Sektion SGMO «Choosing wisely» von Jürg Nadig Schweizer Krebsbulletin 2014; 2:101
2. Nadig J. Choosing wisely, Schweizer Krebsbulletin 2014; 1:74

Dr. Jürg Nadig, Präsident SGMO
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Wir drucken hier die Antwort von Dr. Jürg Nadig auf die Stellungnahme von Prof. M. Fey, die in der letzten Ausgabe des Krebsbulletins erschienen war (S. 101). Journalistische Sorgfalt hätte schon damals verlangt, dass wir dem Kollegen Nadig die Möglichkeit gegeben hätten, auf die Stellungnahme von Prof. Fey in derselben Ausgabe zu antworten. Aus verschiedenen, vor allem zeitlichen Umständen, haben wir dies unterlassen. Dafür entschuldigen wir uns.

Die Redaktion

HPV and cancer: a unique opportunity for cancer prevention

Silvia Franceschi, International Agency for Research on Cancer, Lyon, France

Approximately 610,000 of the 13 million new cancer cases worldwide are attributable to human papillomavirus (HPV).[1] The global attributable fraction (AF) of HPV is 4.8% with 570,000 new cancer cases diagnosed among women (AF: 9.4%) and 39,000 cases among men (AF: 0.6%). HPV is believed to be responsible for 100% of cervical cancers, 88% of anal cancers, 70% of vaginal cancers, 50% of penile cancers, and 43% of vulvar cancers with the majority caused by HPV16 or 18. The corresponding percentage for oro-pharyngeal cancer is less well-defined than for the other anatomic sites due to the still predominant role of tobacco and alcohol use in many populations. The AF of HPV in oro-pharyngeal cancer is estimated to be 26% globally, but the corresponding HPV prevalence rises to ≥50% in Northern Europe, North America, Japan, and Australia.[1]

The AF of HPV in women is much greater in in countries in which cervical screening is inadequate. It ranges from ≤2.5% in North America and Australia to 4.5% in Europe and 25% in sub-Saharan Africa and India. In men, the PAF is highest in India (1.8%) and <1.0% in all other countries or regions.

Cervical cancer is the most important cancer in women in several countries in sub-Saharan Africa and a few ones in Latin America and Asia. Of notice, cervical cancer incidence rates are also very high (>20 per 100,000 women) in many countries, including a few Eastern European countries, in which breast cancer has become more common than cervical cancer.

The knowledge on the carcinogenicity of HPV has rapidly grown in the last three decades and HPV infection with thirteen high-risk HPV types is now recognized to be the necessary cause of cervical cancer and precancerous lesions.[2] This knowledge has paved the way to unique opportunities of prevention through a combination of HPV vaccination and HPV test-based screening.

Currently available (bivalent or quadrivalent) HPV vaccines against HPV16 and 18 can certainly prevent approximately 70% of cervical cancer in every world region.[2] However, cross-protection of current vaccines from other similar types (HPV31, 33, and 45) has been reported and a new vaccine against HPV6/11/16/18/31/33/45/52/58 will soon be marketed raising expectations that a larger fraction of cervical cancers will be eventually prevented.[3] The HPV vaccine has the greatest efficacy in individuals not yet exposed to the virus. The World Health Organization (WHO) therefore recommends including HPV immunization of girls at age 9-to-12 years into comprehensive cervical cancer prevention and control programmes. Major challenges for the introduction of HPV vaccination were the high cost of the vaccine and the need to target adolescent girls, for whom no efficient vaccination platforms were in place. Fortunately, the cost of the vaccine for the public sector is steadily declining. The price of HPV vaccine was, for instance, more than 100 Euro per dose in Europe and North America in 2007 but few years later it has dropped to 30 Euro in Italy, 20 in Sweden, and 13 in Latin America. The vaccine can be currently purchased by the Global Alliance for Vaccines and Immunisation (GAVI) at less than 5 US Dollars per dose: still too expensive compared to other widely used vaccines but approaching the price (approximately 2 Dollars per dose) that would make it very cost-effective in most of the poorest countries.[4] Twenty-one GAVI-eligible countries are expected to benefit from the introduction of the HPV vaccine in 2013-14 (http://www.gavialliance.org). Two pioneer countries, Bhutan and Rwanda, have shown that low-income countries can implement school-based HPV vaccination programmes and achieve even higher coverage (>90%) than high-income countries. HPV vaccination in the two countries is currently monitored by the International Agency for Research on Cancer, Lyon, France.[5]

HPV vaccination with fewer doses has been shown to be non-inferior to vaccination with three doses and the WHO Strategic Advisory Group of Experts on immunization (SAGE) endorsed dose reduction to two doses in April 2014.[6] This change will substantially simplify the logistics and further reduce the costs associated with HPV vaccination.

New opportunities have also become available for secondary prevention of cervical cancer. The disease, the most widely screened cancer worldwide, has a long natural history with slow-progressing precancerous lesions such as cervical intraepithelial neoplasia grade 2 and 3 (CIN2 and 3) and adenocarcinoma *in-situ*. Contrary to breast cancer screening, cervical cancer screening's aim is to detect precancerous lesions instead of cancer and, therefore, screening reduces not only mortality rates but also incidence rates in screened populations. Currently, four main types of tests can be used, mainly depending upon the income level of a country: conventional cytology (Pap smear),

liquid-based cytology, visual inspection with acetic acid (VIA), and HPV testing. They can all identify women with CIN as well as early invasive cancer, if provided with quality assurance and by well-trained providers.

Pap smear screening has been largely responsible for the substantial decline in cervical cancer incidence and mortality in developed countries of Europe, North America, Japan, Australia, and New Zealand in the last five decades. However, quality assurance of cytology is difficult and the test has to be repeated every few years to remedy to a relatively low sensitivity. Four large randomised controlled trials of HPV testing *versus* cytology have been carried out in Italy, the Netherlands, Sweden, and the United Kingdom.[7] A lower CIN3 incidence was recorded after HPV testing compared with cytology. Despite different screening protocols, the relative incidence of CIN3 or worse histological findings after the first screening round was approximately halved in the HPV arm *versus* the cytology arm in all trials. These results show that HPV-based screening detects persistent CIN3 better and earlier than cytology, thus increasing the probability of treatment before invasion. HPV-based screening also provides 60–70% greater protection against invasive cervical carcinomas compared with cytology.[7] Data of the randomised trials supported initiation of HPV-based screening from age 30 years and extension of screening intervals to at least five years.

Cervical screening using HPV testing and, to a lesser extent, VIA has been found to be effective in preventing cervical neoplasia and deaths caused by cervical cancer in clinical trials in Asia[8] and Africa.[9] Recently, the WHO issued new recommendations for cervical cancer screening in women age 30 years or older in low/middle- income countries. Where resources permit, a strategy of screen with HPV tests and treat with cryotherapy (or loop electrosurgical excision procedure, LEEP, when not eligible for cryotherapy) or a strategy of screen with HPV testing followed by VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) are preferable compared to a strategy of screen-and-treat with VIA.[10]

In conclusion, HPV vaccination and HPV-based screening have the potential to attain a nearly complete elimination of cervical cancer in the new generations of vaccinated women and to avoid of the vast majority of cervical cancer deaths in unvaccinated women. HPV vaccination will allow a gradual reduction of screening frequency and the cost and anxiety related to the detection and treatment of precancerous lesions. Priorities in low/middle-income countries include access to cheaper HPV vaccines and HPV tests and the establishment of adequate infrastructures for screening and vaccination. In many high-income countries major challenges include overcoming socio-cultural inequalities in screening and improving the coverage of HPV vaccination that is at present sub-optimal (≤50% in France, Germany, and Switzerland) due to organizational problems, complicated reimbursement schemes, and unfortunate misperception of the risk/benefit ratio of vaccination.

Conflict of interest: No potential conflict of interest is disclosed by the author.

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PARP inhibitors – the next standard of care in ovarian cancer?

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PARP inhibitors – the next standard of care in ovarian cancer?

These are exciting times for the treatment of ovarian cancer as strategies incorporating molecular targeted therapies are proving successful (1). The majority of women continue to be diagnosed with advanced disease and the overall 5-year survival rate is around 40-50%. The international standard of care for newly diagnosed ovarian cancer is a combination of optimal cytoreductive surgery and platinum-based chemotherapy. However, there remains a significant risk of recurrence and drug resistance at which stage, the condition is not curable.

There has been an explosion in our understanding of the biology of ovarian cancer and drug development in recent years. Molecularly targeted agents hold the promise of greater selectivity and hence increased efficacy associated with lower toxicity than traditional chemotherapy. Targeting angiogenesis and DNA repair pathways are two intensively exploited areas. Here, we summarise the key results and concepts of PARP inhibitors.

There are distinct DNA repair pathways that exist to repair DNA lesions which are essential for cell viability (2). *BRCA1* and *BRCA2* are critical for the maintenance of genome integrity. They are important for the DNA repair of double-strand breaks (DSBs) using the homologous recombination (HR) pathway. Cancer cells that are deficient in BRCA1 or BRCA2 function utilise alternative pathways for the repair of DSBs, such as non-homologous end-joining (NHEJ) which leads to chromosome instability. This is increased by DNA-damaging agents such as platinum that induce DSBs leading to chemosensitivity.

PARP (Poly ADP ribose polymerase) inhibitors have shown exceptional activity in women with *BRCA* mutation–associated ovarian cancer and represent a therapeutic approach that exploits the concept of «synthetic lethality» - the situation where two defects acting individually have little effect, but when combined become lethal. PARP inhibitors block PARP proteins which facilitate the repair of single-strand DNA breaks (SSBs). This leads to accumulation of SSBs and can generate DSBs that require repair by HR. Therefore, when PARP inhibitors are used in a HR deficient background (such as *BRCA*1 or *BRCA*2 mutation), this results in the generation of DNA lesions that cannot be effectively repaired, leading to cell cycle arrest and/or cell death.

In addition to germline *BRCA*1 and *BRCA*2 mutations, there are other causes of HR deficiency that can result in cancers having *BRCA*-like behaviour - a phenomenon termed '*BRCA*ness' (3). These include somatically acquired *BRCA1/2* mutations, *BRCA* methylation (epigenetic silencing) and dysfunction of other genes involved in HR. Up to 50% of patients with high grade serous ovarian carcinoma (HGSOC) show HR deficiency (4). The majority of ovarian cancer cases are sporadic with approximately 10% considered familial. Up to 90% of hereditary ovarian cancer cases are caused by mutations in *BRCA*1 or *BRCA*2. Furthermore, over 15% of sporadic cases of HGSOC (without a family history) are associated with a germline *BRCA* mutation (5).

Evidence to support the treatment of *BRCA*-deficient tumours with PARP inhibitors was demonstrated in landmark preclinical studies (6) which led to the concept being developed into clinical trials.

In 2009 Fong et al (7) reported results from a phase 1 study for the PARP inhibitor, olaparib in a group of patients with advanced solid tumours enriched for the presence of a *BRCA1/2* mutation. The drug was generally well tolerated with minimal adverse effects (mostly gastroinstestinal and fatigue) and encouraging single-agent anticancer activity in *BRCA*1/2 mutation carriers; 9/19 (47%) partial responses, including 8 patients with ovarian cancer; 63% (12/19) derived clinical benefit from olaparib, providing proof of concept in the clinic for synthetic lethality. The study was expanded to include 50 patients with *BRCA*1/2 ovarian cancer (8). Of note, the results suggested that responses to PARP inhibition decreased with platinum resistance, with clinical benefit rate of 69% for platinum-sensitive, 45% for platinum-resistant and 23% for platinum-refractory disease.

These encouraging results led to the development of phase II studies in ovarian cancer. Audeh et al demonstrated efficacy (33% RECIST response at 400 mg bd) and tolerability of olaparib in germline *BRCA*-mutated recurrent ovarian cancer which included platinum-resistant patients (9). Gelmon and colleagues provided evidence for a wider use of PARP inhibitors based on the fact that up to 50% of high-grade serous, sporadic ovarian cancers have defective HR. In this study patients with high-grade serous ovarian cancer without germline *BRCA*1/2 mutations also achieved clinical responses (50% in platinum-sensitive group (10).

Given the encouraging tolerability and efficacy, the next step was to pursue PARP inhibitors as maintenance therapy. In a randomised, double-blind, placebo-controlled phase 2 trial in which patients with platinum-sensitive, recurrent, high-grade serous ovarian cancer were randomised to either olaparib or placebo maintenance therapy (following a response from their most recent platinum-based regimen), olaparib maintenance treatment significantly improved progression-free survival (median 8.4 months vs. 4.8 months (HR 0.35, p<0.0001)). An interim analysis has shown no overall survival benefit so far (11). Amongst *BRCA* mutated patients, the median PFS was significantly longer in the olaparib group than in the placebo group (11.2 months vs 4.3 months HR 0.18, p<.0001). Benefit was also seen in the *BRCA* non-mutated group although the magnitude of PFS prolongation was less (7.4 vs 5.5 months; HR 0.54, p=0.008). The lack of overall survival benefit so far (data immature) may be in part due to the fact that a significant proportion of patients in placebo group received a PARP inhibitor post-progression.

Several phase III studies (eg. SOLO1, SOLO2, ARIEL3 and NOVA) are currently addressing maintenance PARP inhibitors in *BRCA* and non-*BRCA* mutated ovarian cancer.

Combination strategies of PARP inhibitors with chemotherapy, radiotherapy or other targeted agents are under evaluation. A potential limitation is increased myelosuppression with chemotherapy. The preliminary results of the first randomised study of a PARP inhibitor (olaparib) in combination with an antiangiogenic agent (cediranib) in platinum-sensitive ovarian cancer were presented at ASCO 2014 (12). There was a significant improvement in the median PFS (17.7 months vs 9.0 months HR 0.42, p=0.005) and response rate (80% vs 48%, p=0.002) for the olaparib/cediranib arm compared to olaparib alone. Grade 3/4 toxicity was signficantly higher for patients in the combination arm (70% vs 7%) (12). Studies evalating PARP inhibitors with PI3kinase pathway agents are underway.

There are approximately 40 clinical trials of PARP inhibitors ongoing. Table 1 lists the phase II/III trials in ovarian cancer. Important issues for the development of PARP inhibitors are patient selection (*BRCA* mutated only or wider population?) and drug resistance. Key questions include: Single agent PARP inhibitors versus combination strategies? When is the best time to use PARP inhibitors?- maintenance vs treatment, first line vs recurrent disease, platinum-sensitive vs role in platinum-resistant disease?

	PARP inhibitor	Clinical Trial Phase	Indication	ClinicalTrials.gov Identifier
Single agent	Olaparib	III	SOLO-2: Maintenance treatment in relapsed platinum-sensitive disease	NCT01874353
	Olaparib	III	SOLO-1: Maintenance monotherapy following first line platinum-based chemotherapy.	NCT01844986
	E7449	I/II	Single agent treatment in platinum sensitive/resistant ovarian cancer	NCT01618136
	BMN 673	I/II	Single agent treatment in platinum –sensitive disease	NCT01989546
	Niraparib	III	NOVA: Maintenance monotherapy following chemotherapy in platinum-sensitive relapsed disease	NCT01847274
	Veliparib	I/II	Single agent treatment in platinum-resistant or partially platinum-sensitive relapse	NCT01472783
	Rucaparib	I/II	Single agent treatment in platinum-sensitive disease	NCT01482715
	Rucaparib	II	ARIEL-2: Single agent treatment in platinum-sensitive relapsed disease	NCT01891344
	Rucaparib	III	ARIEL-3: Maintenance monotherapy following chemotherapy in platinum-sensitive relapsed disease	NCT01968213
Chemotherapy combination	Veliparib	I/II	Combination treatment with Topotecan in relapsed or refractory disease	NCT01012817
Targeted agents combination	Olaparib	I/II	Combination treatment with Cediranib Maleate (VEGFR inhibitor) in recurrent/metastatic diesease	NCT01116648

Table 1: Phase II/III clinical trials of PARP inhibitors in ovarian cancer.

An application for the use of olaparib in *BRCA* mutated platinum-sensitive ovarian cancer has already been submitted to the European Medicines Agency (based on the phase II results). Hopefully, PARP inhibitors will be standard of care for *BRCA* mutated ovarian cancer in 2015.

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The working group Gynecological tumors of the SAKK: so far so good!

Cristiana Sessa, Co President of the WG Gynecological tumors

There has always been a remarkable interest for gynecological tumors in the Swiss Group for Clinical Cancer Research (SAKK). The first successful results, which were published in Cancer, were achieved already in the 45/81 study (Melphalan IV and cisplatin in stage III-IV ovarian cancer) chaired by A. Goldhirsh. Despite this success, and because of a variety of reasons ranging from changes in the membership to lack of interesting studies, from low patients' accrual to competition with the private sector, the activity and the interest for the group steadily decreased until its end in 2003.

Since 2009, however, a lively discussion was carried out in the SAKK board in order to explore the possibility of resurrecting the group. The result was the proposal of a new structure which could reflect the multimodal approach of gynecological cancers and the well established clinical situation of a joint clinical management with gynecologists and gyneco-oncologists.

The development of a working group composed by medical oncologists and gyneco-oncologists was proposed by the President of the SAKK Prof. B. Thürlimann to Prof. D. Fink, President of the Swiss AGO Group, who accepted it.

The start

On the 26th November 2011, during the semiannual meeting of the SAKK in Basel, the new working group, called *Gynecological Tumors Group*, was founded. The first meeting of the new group was attended by many new participants and the discussion was intense. Prof. B. Thürlimann presented the *Gynecological Tumors Group* to the audience and Prof. C. Sessa introduced its aims.

Prof. C. Sessa (SAKK) and PD M. Fehr (AGO) were appointed representatives of the Group. They were responsible for the organization of the next steps, namely the preparation of new proposals for the SAKK Board, the organization of future meetings, and so on. Moreover, they were the contact persons between the SAKK and the Group.

The Group discussed the INOVATYON trial (a trial concerning ovarian cancer sponsored by the group Mango in Italy), which was presented to the SAKK board for final assessment in January 2012; moreover three other trials of the ENGOT group were discussed. The Group wished that SAKK joined an international group such as ENGOT* or ICON.

Current situation (June 2014)

Fourteen (out of 22) SAKK centers are today participating in the Group: for each center a team of one dedicated medical oncologist and one gynecologist has been identified and is of reference to the Group.

The application for membership to ENGOT was accepted in January 2014. The Gynecogroup is participating to two studies, the ENGOT-ov17 Mito 16/Mango and the ENGOT-ov 5 Inovatyon in ovarian cancer:

- The MITO-16/MANGO-ENGOT-ov17 study is an academic phase III study promoted by the University of Naples to evaluate, in patients with platinum sensitive ovarian cancer, whether the continuation of Bevacizumab, which was part of the initial treatment, is of benefit at the time of the first recurrence. The study commitment is of 400 patients over 24 months. The SAKK declared an accrual of 30 patients.

- The Inovatyon ENGOT-ov5 study is an academic phase III study promoted by the Italian MANGO group to compare the efficacy of a combination with platinum versus a combination without platinum in the 2nd-3rd treatment of partially platinum sensitive ovarian cancer patients. The study commitment is of 588 patients over 3.5 years, the SAKK declared an accrual of 40 patients.

In addition, the group is participating to the AGO project for a registry on quality of surgery in ovarian cancer.
Future plans include the active participation to the translational working group of ENGOT, the development of

phase II studies with new antitumor drugs, the participation to first line international phase III studies in ovarian cancer and the implementation of other new ENGOT studies, in particular in endometrial and cervical cancer.

Collaboration with international groups is essential for keeping alive the group and for making members aware of the most recent achievements in gyneco-oncology.

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ENGOT (European Network of Gynecological Oncological Trial Groups) is a network of national and regional clinical trial units that coordinates and promotes clinical trials in Europe in patients with gynecological cancers. This coordination is relevant for academic clinical trials, translational research and research on rare diseases and for company-sponsored clinical trials to perform multinational studies in Europe. The ultimate goal is to bring the best treatment to gyneco cancer patients through the best science, and enabling every patient in every European country to access a clinical trial. Currently 20 European cooperative groups are participating to ENGOT studies.

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Referenzen: 1. Spezialitätenliste BAG, www.spezialitaetenliste.ch; Stand Mai 2014. **2.** Tafinlar® (Dabrafenib) Arzneimittelinformation: www.swissmedicinfo.ch

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Brustkrebs und Sexualität: Eine Übersicht

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Brustkrebs ist die häufigste Krebserkrankung der Frau, und weiterhin nehmen die Krankheitsfälle zu. Erfreulicherweise haben Früherkennung und innovative Behandlungsmöglichkeiten die Prognose in den letzten Jahrzehnten deutlich verbessert, so dass die psychosozialen Konsequenzen der Erkrankung und somit die Lebensqualität der sogenannten «Survivors» in den Fokus rücken. Dazu gehört auch die zunehmende Beachtung des Einfluss von Brustkrebs und dessen Behandlung auf die Sexualität der betroffenen Frau. Die Brust gilt in unserer Gesellschaft seit jeher als ein Symbol der Weiblichkeit, sexuellen Attraktivität und Fruchtbarkeit. So erleben die Frauen nebst der Erschütterung durch die potentiell lebensbedrohliche Erkrankung den Brustkrebs als direkten Angriff auf die eigene Erotik. Dass sich dies folglich auch störend in der individuell gelebten Sexualität und Partnerschaft auswirken kann, erstaunt nicht.

Wie beeinflusst die Brustkrebserkrankung sowie deren Behandlung die weibliche Sexualität?

Im Vordergrund stehen häufig sexuelle Funktionsstörungen durch die adjuvanten Therapiemassnahmen. Ebenso fühlt sich die Frau durch den schmerzlich empfundenem Verlust an weiblicher Attraktivität und Erotik in ihrer sexuellen Identität getroffen. Das Gefühl «keine vollwertige Frau mehr zu sein» begründet sich durch den Verlust der Körperintegrität nach Operation sowie die oft vorzeitig herbeigeführte Menopause mit Sistieren der Blutungen und Unfruchtbarkeit. Hinzu kommen gegebenenfalls passagere Veränderungen des Erscheinungsbildes wie Alopezie, Verlust der Wimpern und Schamhaare sowie Gewichtsveränderungen unter Chemotherapie. Nachweislich haben alle diese Faktoren einen negativen Einfluss auf das sexuelle Erleben wie auch die sexuelle Zufriedenheit der Frau. Die Krankheit trifft immer auch das Umfeld und insbesondere den Partner der von Brustkrebs betroffenen Frau. Dieser spielt nicht nur eine bedeutende Rolle in der Unterstützung der erkrankten Partnerin, sondern erfährt selbst eine emotionale Belastung. Die Angst durch die ungewisse Prognose der Krankheit sowie neue Verpflichtungen im Rahmen der Fürsorge stehen im Vordergrund und verdrängen das Verlangen nach Intimität. Diese rücksichtsvoll intendierte Zurückhaltung des Partners wird oft von der Frau als Abweisung erlebt, die sie als Bestätigung, nicht mehr begehrenswert zu sein, interpretiert. Die Spontaneität und Leichtigkeit im Umgang des Paares miteinander geht verloren und führt dazu, dass nicht nur jede Form von Sexualität, sondern auch Zärtlichkeit und Körperkontakt vermieden werden und die Distanz auch emotional erlebt wird.

Eine spezielle Risikokonstellation: die junge Brustkrebspatientin

Es gilt zu beachten, dass insbesondere die junge Brustkrebspatientin ein erhöhtes Risiko für sexuelle Störungen aufweist. Obwohl glücklicherweise in der Minderzahl, müssen sich diese Frauen mit zusätzlichen Schwierigkeiten auseinandersetzen. Das junge Erkrankungsalter bedingt häufiger eine intensive Chemotherapie, eventuell in Kombination mit einer zunehmend längerdauernden Antihormontherapie und dem Risiko der konsekutiven Ovarialinsuffizienz. Oft ist die Familienplanung zum Zeitpunkt der Diagnose nicht abgeschlossen, oder es besteht gar keine feste Partnerschaft. Die Partnersuche für die Single-Frau mit einer Brustkrebsdiagnose in der Biographie wird noch schwieriger, als sie schon war. Dazu haben junge Frauen noch keine Erfahrungen mit körperlichen Altersveränderungen und akzeptieren ihren durch die chirurgische Therapie versehrten Körper mit grösserer Mühe. Nicht selten müssen sich diese Frauen noch zusätzlich der Frage nach einer genetischen Mutation stellen mit der emotionalen Belastung einer Testung und deren Konsequenzen.

Was sind die häufigsten sexuellen Störungen bei Brustkrebs?

Die hohe Störanfälligkeit der Sexualität in der bereits gesunden Bevölkerung erstaunt nicht, dass sich diese durch die schwere Erkrankung noch deutlicher zeigt. Bis zu 70% der betroffenen Frauen geben eine Verschlechterung ihres sexuellen Lebens an. Am häufigsten wird eine Abnahme des sexuellen Verlangens beklagt, Erregungsstörungen und Schmerzen beim Verkehr schliessen sich an und seltener kommt es auch zu Schwierigkeiten, einen Orgasmus zu erlangen oder dessen komplettem Ausbleiben. Der Leidensdruck der Frauen ist unterschiedlich ausgeprägt in Abhängigkeit vom Beziehungsstatus, der Partnerschaftdauer und nicht zuletzt dem Alter der Patientin.

Den grössten Einfluss auf die Frequenz und Intensität von sexuellen Funktionsstörungen hat der Einsatz der Chemotherapie in der Brustkrebsbehandlung. Nebst der transienten oder permanenten iatrogenen Menopause mit lokaler Atrophie, leiden die Frauen häufig zusätzlich unter Erschöpfung, Nausea und rezidivierenden Vaginalinfektionen bei Immunsuppression. Nicht zu unterschätzen sind ebenso Alopezie, Verlust der Wimpern und Brauen sowie die häufige Gewichtszunahme, welche die Krankheit sichtbar und öffentlich

machen, während sich die Narben nach Operation besser verdecken lassen.
Die alleinige antihormonelle Therapie wird meist als weniger belastend erlebt, insbesondere bei bereits vor der Erkrankung erreichter Menopause. Im Vordergrund stehen Schmerzen beim Geschlechtsverkehr durch den lokalen Hormonentzug und eine verminderte Lubrikation, welche als direkte Konsequenz einen Verlust des sexuellen Verlangen nach sich ziehen. Es erstaunt nicht, dass Aromatasehemmer deutlich mehr sexuelle Probleme verursachen als Tamoxifen, welches zumindest durch den partiellen Oestrogen-Effekt weniger lokal atrophierend wirkt.
Der Einfluss der chirurgischen Brustkrebsbehandlung ist weniger eindeutig. Entgegen der gängigen Vorstellung werden sexuelle Funktionsstörungen weniger durch den Operationsmodus, sondern deutlicher durch die medikamentöse Therapie (insbesondere Chemotherapie) beeinflusst. Unbestritten hat die Wahl des operativen Vorgehens jedoch einen wesentlichen Einfluss auf das Körperbild und auf die emotionale Verarbeitung der iatrogenen Veränderung sowie auf das Sexualverhalten und die Lebensqualität der betroffenen Frau. Gerade in unserer Gesellschaft, die den Wert einer Frau an Jugend und Schönheit misst, leiden insbesondere die jüngeren Patientinnen an der verlorenen Unversehrtheit ihres Körpers. Einige Studien konnten eine grössere Beeinträchtigung der Sexualität bei Mastektomie gegenüber der Brusterhaltung zeigen, insbesondere bei Frauen, welche ihr Selbstbild in hohem Mass auf ihre äusserliche Erscheinung abstützen. Der Einfluss der Brustrekonstruktion wird trotz des deutlichen Vorteils durch Verzicht auf eine externe Prothese und flexiblere Kleiderwahl eher überschätzt. Die Frauen empfinden die rekonstruierte Brust zwar als «Silhouetten-Korrektur», eine «Ich-Zugehörigkeit» fehlt hingegen häufig, nicht zuletzt auch durch den Sensibilitätsverlust der einst erogenen Zone. Objektiver Befund und subjektive Befindlichkeit können postoperativ deutlich auseinander klaffen, was manchmal von ärztlicher Seite schwer zu verstehen ist. Ein wichtiger protektiver Faktor für die Anpassung an ein verändertes Körperbild ist der Miteinbezug der Patientin in den Entscheidungsprozess über das operative Vorgehen.

Zur vorherrschenden Praxis der Sexualberatung bei Brustkrebs

Obwohl Sexualität in unserer Gesellschaft heute sehr präsent ist, bleibt das eigene Sexualleben ein sehr persönliches Thema. Insbesondere sexuelles Versagen wird tabuisiert. Auch in der Beziehung zwischen Arzt und Patientin findet das Gespräch über sexuelle Folgen der Brustkrebsdiagnose wenig Platz, obwohl von Seiten der Frauen ein grosses Bedürfnis besteht. Nicht nur in der frühen Phase der Diagnose und Primärbehandlung, wo das Thema vielleicht vernachlässigbar erscheinen mag, sondern auch in der Nachsorge wird die Patientin häufig nicht auf eine mögliche Veränderung der Sexualität angesprochen. Als Gründe dafür geben Ärzte ungenügende sexualmedizinische Kenntnisse, Zeitmangel aber auch Hemmungen, dieses heikle Thema anzusprechen, an. Es wäre jedoch wünschenswert, dass das behandelnde Team über mögliche Auswirkungen der Erkrankung und deren Behandlung auf das Sexualleben aufklärt wie über jede andere Nebenwirkung auch. Wenn Patientinnen die Gesprächsbereitschaft ihres behandelnden Arztes für sexuelle Anliegen erleben, fühlen sie sich entlastet und haben auch zu einem späteren Zeitpunkt die Möglichkeit darauf zurückzukommen. Selbstverständlich gehört die Aufklärung über mögliche supportive Massnahmen, insbesondere in Bezug auf die genitale Atrophie, dazu. Besonders wichtig ist das Angebot, auf Wunsch den Partner in die Beratungsgespräche einzubeziehen. Die häufig eingeschränkte Kommunikation über sexuelle Probleme und Wünsche kann so in einem sicheren Rahmen in Richtung einer grösseren Offenheit gefördert werden. Manchmal reicht ein stützendes ärztliches Gespräch nicht aus, insbesondere bei bereits vor der Brustkrebsdiagnose bestehender sexueller Unzufriedenheit oder Paarproblematik. Hier ist eine Überweisung an einen sexual- und paartherapeutisch erfahrenen Psychotherapeuten oder Sexualmediziner sinnvoll.

Ich danke Herrn Prof. Dr. phil. U. Clement, Leiter des Instituts für Sexualtherapie Heidelberg für das sorgfältige Durchlesen des Artikels und seine konstruktiven Anregungen.

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Symptomassessment und -management bei Frauen mit vulvären Neoplasien

Status quo und künftige Entwicklungen

Andrea Kobleder, Silvia Raphaelis, Beate Senn

Ein systematisches Symptomassessment bildet bei Frauen mit vulvären Neoplasien die Basis für ein optimales Symptommanagement. Der Einbezug der Patientinnensichtweise ist die Bedingung für einen effektiven Betreuungsprozess.

Frauen mit vulvären Neoplasien stellen unter den Patientinnen mit gynäkologischen Tumoren eine vergleichsweise kleine Gruppe dar. Die Inzidenzrate von Vulvären Neoplasien, welche vulväre intraepitheliale Neoplasien (VIN) und das Vulvakarzinom beinhalten, beträgt in Deutschland und der Schweiz ungefähr 2-7 pro 100.000 Frauen pro Jahr (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, 2010). In der Therapie dieser Erkrankung konnten in den vergangenen Jahren große Fortschritte erzielt werden (Gray, 2010). Da die minimal invasive Chirurgie jedoch ebenfalls vielfältige postoperative Symptome verursachen kann (Kaushik, Pepas & Nordin, 2011) und zu vergleichsweise kurzen Krankenhausaufenthalten führt (Oncosuisse, 2011), müssen die Patientinnen über die Entlassung hinaus bestehende oder später auftretende Symptome selbst beobachten, einschätzen und behandeln sowie hierfür notwendige Symptommanagement-Kompetenzen innerhalb kurzer Zeit erlernen.

Der erste wesentliche Schritt für ein optimales Symptommanagement ist eine systematische Symptomerfassung. Diese kann grundsätzlich aus einem klinischen Assessment durch Fachpersonen und/oder den Berichten der Patientinnen selbst über ihre Gesundheit bzw. Symptome (patient reported outcomes = PRO) bestehen. Da Frauen mit vulvären Neoplasien ihre postoperativen Symptome nach der Entlassung überwiegend selbst behandeln müssen und Symptome in der klinischen Praxis häufig unterschätzt werden, ist hier vor allem eine selbsteinschätzende Symptomerfassung relevant. Denn diese kann grundlegende Informationen aus der Perspektive der Patientinnen über die Wirksamkeit und die Konsequenzen der Symptombehandlung liefern. Bislang stand jedoch kein entsprechendes Assessmentinstrument für diese Patientinnen zur Verfügung. Deshalb wurde im Jahr 2010 mit 20 Betroffenen und 9 Fachexpertinnen und -experten das WOMAN PRO Symptomtagebuch entwickelt.

Andrea Kobleder

Beate Senn

Silvia Raphaelis

Frauen mit vulvären Neoplasien können mit diesem Instrument erstmals ihre Erfahrungen nach einem chirurgischen Eingriff standardisiert einschätzen. Zusätzlich kann es im klinischen Assessment zur systematischen Erfassung von zentralen Symptomen und Informationsbedürfnissen unterstützend zum Einsatz kommen. Das Instrument verfügt über eine hervorragende Inhaltsvalidität (CVI=1.0) und lässt eine reliable Messung der Symptomerfahrung (wundbedingte Symptome: α = 0.81, Schwierigkeiten im täglichen Leben: α = 0.74 und psychosoziale Symptome: α = 0.90) zu (Senn et al., 2012).

Darüber hinaus kann das Assessment-Tool in Studien als Messinstrument der Symptomprävalenz und -erfahrungen eingesetzt werden. Hierzu wurde es erstmals im Rahmen eines Mixes-Methods Projektes mit 65 Frauen mit vulvären Neoplasien aus jeweils vier Kliniken in der Schweiz (Zürich, Basel, Bern, St. Gallen) und in Deutschland (Berlin, Düsseldorf, Freiburg, München), welche dort zwischen Oktober 2010 und Oktober 2011 behandelt wurden, genutzt. Die durchschnittliche Anzahl der Symptome lag bei 20,2 (Standardabweichung 5.77), pro Patientin wurden 5 bis 31 Symptome angegeben. Die drei häufigsten wundbedingten Symptome waren «Schwellung» (n=56), «Flüssigkeitsaustritt» (n=54) und «Schmerz» (n=52), während bei den Schwierigkeiten im Alltag «Sitzen» (n=63), «Kleider tragen» (n=56) sowie «Ausführen der Alltagstätigkeiten» (n=51) und bei den psychosozialen Problemen «Müdigkeit» (n=62), «Unsicherheit» (n=54) und «Gefühl, dass sich der Körper verändert hat» (n=50) am häufigsten auftraten (Senn et al., 2013).

Zukunftsoptionen für Frauen mit vulvären Neoplasien

Die hohe Anzahl an belastenden postoperativen Symptomen unterstreicht die Wichtigkeit eines strukturierten Assessments im Rahmen regelmässig stattfindender

Follow-Up Termine zwischen den Patientinnen und dem interprofessionellen Team. Eine Kombination aus PRO- und klinischem Assessment kann massgeblich zur Verbesserung der Situation betroffener Frauen beitragen und Hinweise zu Massnahmen, die das Selbstmanagement unterstützen liefern. Um das Wissen, die Motivation und die Handlungen der Patientinnen zu unterstützen, empfehlen wir eine Beratung durch eine/n Pflegeexpertin bzw. -experten. Diese Beratungen sollten komplementär zu den ärztlichen Konsultationen stattfinden und können einen wichtigen Beitrag zur optimierten Symptombehandlung und Früherkennung von Komplikationen liefern. Zurzeit wird in einem internationalen Projekt der Fachhochschule St.Gallen, der WOMAN PRO II Studie (Clinical Trial ID: NCT01986725) ein komplexes Beratungsprogramm durch eine Pflegende mit erweiterte bzw. spezieller Expertise, einer sogenannten Advanced Practice Nurse (APN) getestet. Die Studie wird von 2013 bis 2016 in der Schweiz, in Österreich und Australien durchgeführt. Um die Qualität der pflegerischen Beratung zu definieren, wurden clinical pathways für die Patientinnen beschrieben und eine evidenzbasierte Leitlinie mit 44 Empfehlungen entwickelt. Die Empfehlungen fokussieren die Themenbereiche Symptom Selbst-Assessment, Operationswunde und Vulvapflege, postoperativer Schmerz, postoperative Müdigkeit, postoperative Miktionsprobleme, Schwierigkeiten beim Sitzen, Kleider tragen sowie beim Ausführen alltäglicher Handlungen, Lymphödem, Unsicherheit und Körperbild.

Nebst der Überprüfung der Wirkung der Beratung soll eine Kosten-Nutzen-Analyse erfolgen. Ziel dieser Analyse ist, relevante wirtschaftliche Fragestellungen im Rahmen der WOMAN PRO II Studie zu beantworten. Es soll dargelegt werden, welche Kosten für unterschiedliche Betreuungsansätze aufgewendet werden müssen und welche Betreuungsart zu weniger postoperativen Beschwerden führt.

Ferner wird insbesondere für jüngere Patientinnen eine Web-Applikation (App) entwickelt. Sie soll den Patientinnen zusätzlich zum persönlichen Kontakt mit den Gesundheitsfachpersonen aktuelles und verlässliches Wissen zur Erkrankung rund um die Uhr niederschwellig und unabhängig zur Verfügung stellen. Die App könnte die Patientinnen hierdurch nicht nur in ihrem Selbstmanagement und ihrer Lebensqualität unterstützen, sondern auch die Hürde über eine zumeist tabuisierte Erkrankung zu sprechen, minimieren. Durch eine Social Network Funktion haben die Patientinnen ausserdem die Möglichkeit, mit anderen Betroffenen in Kontakt zu treten und Erfahrungen auszutauschen.

Die genannten Projekte unterstützen Frauen mit vulvären Neoplasien in ihrem Symptommanagement und tragen zur Enttabuisierung der Erkrankung bei.

Die Autorinnen bedanken sich bei allen Beteiligten, die für das Gelingen des Projektes wesentlich waren und sind. Besonderer Dank gilt den Patientinnen für ihre Offenheit, den Fachpersonen und Kliniken für die Unterstützung bei der Datensammlung, den IT Expertinnen und -experten für die Weiterentwicklung des Symptom-Assessment-Tools, und den Gesundheitsökonomen für die Planung der Kosten-Nutzen-Analyse.

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Multidisciplinary management of bone metastases in advanced cancer care

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Introduction

Bone metastases represent a frequent and challenging clinical problem in the field of advanced cancer disease and the most common cause of cancer-related pain. According to the tumour type, their incidence may rank from 40% (lung, kidney) up to 70% (prostate and breast cancer) but major concerns also exist for many other cancer types [1]. Pathophysiologically three different types of bone metastases can be characterized, resulting in different radiological features: osteoblastic (high bone tissue density), osteolytic (low bone tissue density) and «mixed type» metastases. Over their prognostic significance inside the disease course, bone metastases usually generate problems and complications that may produce a significant impact on quality of life (pain, fractures) or even be life threatening under some circumstances (hypercalcemia, fractures, spinal cord compression). Furthermore they still represent a significant cause of increased medical consultations, emergency room and hospital admissions. Their onset may interfere with or even delay the timing of an appropriate administration of cancer therapies.

Following these and other reasons, an early, proper and unavoidably multidisciplinary management of this oncological challenge and of its related complications, should be considered mandatory in the modern cancer medicine.

Pathophysiology

Osteolytic metastases are characterized by the release of osteoclastogenic agents by tumor cells in the bone microenvironment and the osteoblastic metastases are a direct consequence of the release of factors that stimulate osteoblast proliferation, differentiation and subsequently uncontrolled bone formation by metastatic cancer cells [2]. More recent studies have highlighted the importance of the bone microenvironment and the interactions with tumor cells. To generate bone metastases, cancer cells must intravasate and survive into circulation, attach to the vascular endothelium, extravasate and proceed with colonization into the bone. The bidirectional interaction of bone cells with cancer cells in the production of bone metastases is characterized by a complex release of osteolytic mediators, such as TGF-β, parathyroid hormone related peptide (PTHrP), RANKL, proteases like cathepsins and matrix metalloproteinases, and osteoblastic mediators with a large variety of growth factors. Fibroblast-, platelet- and insulin-like growth factors, are important actors known in the metastasizing process [3, 4, 5].

Diagnosis and imaging

Diagnostic imaging has a primary role in the detection, diagnosis, treatment planning and, later, follow-up of bone metastatic disease. Secondary bone lesions can be found at every site, but more often, in decrescent percentage, in vertebrae, pelvis, proximal femur and proximal humerus and skull. Other diagnostic modalities are in the field of Nuclear Medicine: Technetium-99m (^{99m} Tc) scintigraphy and fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning.

Plain X-ray film is an easy and low cost imaging method, with good specificity but low sensibility to bone lesions [6]. Lesions can appear as osteolytic, osteosclerotic or mixed lesions, often suggesting the nature of the primary tumor. While plain film is of low utility in the detection of new lesions, it remains a good instrument in the follow-up of known lesions especially in peripheral sites.

Computed Tomography (CT) is far much superior to plain film in the detection of bone lesions but has low sensitivity to early lesions, that only involve bone marrow. The use of contrast media can give some more information, especially on associated masses, in particular about the relationships with adjacent vessels and nerves, but in any case sensitivity remains low. Metser et al. [7] made a retrospective review to compare CT and FDG-PET in the assessment of secondary malignant involvement of the spinal column. Of 242 lesions detected on PET/CT, PET identified 220 lesions and CT identified 159. For both PET alone and CT alone specificity was 56%. On a patient-based analysis, the sensitivity of PET and of PET/CT for the detection of spinal metastasis was 98% and 74%,

respectively (P<0.01). FDG-PET was more sensitive than CT in detecting spinal metastases in patients with known spinal metastases. One major drawback of CT is the relatively high radiation dose; on the other hand neoplastic patients undergo staging CT examinations that usually covers the greatest part of the axial skeleton. Moreover CT is the best imaging modality for a guided biopsy of bone lesions and it is always needed when planning some interventional procedures as cementoplasty (see later).

Magnetic Resonance (MRI) has very high sensitivity to bone lesions: the routinary use of T1w, T2w and STIR images gives high sensitivity and high specificity to MRI examinations in which bone lesions are usually hypointense in T1w images and hyperintense in T2w; results are better if Gadolinium (Gd) enhanced T1 Fat Suppressed images are taken with variable but usually high degree of contrast enhancement. MRI depicts early hematogenous dissemination of the tumor to the bone marrow before reactions in the adjacent bone are detectable even on ^{99m} Tc scintiscans (sensitivities of 91.4% for MRI and 84.8% for bone scintiscanning) [8]. Flickinger and Sanal [9] reported sensitivities of 100% for MRI and 62% for scintiscanning while specificities was of 62% for MRI and 100% for scintiscanning. Eustace et al. [10] reported for MRI and scintiscans, respectively, sensitivities of 96.5% and 72%, specificities of 100% and 98%, and positive predictive values of 100% and 95%. Lauenstein et al. [11] compared the results of whole-body MRI in patients with tumors, with staging based on results of CT, dedicated MRI, and nuclear scintigraphy as standards of reference. Whole-body MRI revealed sensitivity and specificity values of 100%. It was more sensitive in the detection of hepatic and osseous metastases than were the reference techniques.

In *Nuclear Medicine*, ^{99m} Tc bone scintigraphy and FDG-PET CT scanning are both effective methods in the research of occult secondary bone lesions. In case of an aspecific finding an imaging procedure is needed (plain film, CT or MRI depending on site and dimensions of the suspected bone lesion) to confirm and characterize the lesions. Both procedures have great sensitivity (higher for FDG PET-CT) but often low specificity and poor spatial resolution so that complementary CT or, better, MRI examinations are required to localize and qualify areas of increased uptake. In a comparative study of MRI, FDG PET and ^{99m} Tc bone scintigraphy Daldrup-Link et al. [12] found sensitivities of 90% for FDG-PET scanning, 82% for whole-body MRI, and 71% for^{99m} Tc bone scintiscanning. FDG-PET scanning shows a high number of false-positive lesions, which require follow-up imaging with other modalities. The use of semi-quantitative criteria for tumor FDG uptake in the qualitative evaluation of images may increase the specificity. In skull metastases, the high rate of glucose metabolism in the normal areas of brain may obscure metastases.

Management

The management of bone metastases evolved dramatically in the last decades, becoming a field where the application of multidisciplinary competences represent a model for other fields of oncology. In the following text we will focus on some aspects of the multimodal approach and review the current status of scientific evidence.

Radiotherapy

Radiotherapy and in particular External Beam Radiotherapy (EBRT) is a widely accepted and effective way to palliate pain caused by bone metastases. It has few side effects and can provide significant palliation of painful bone metastases in up to 60-70% of cases. Its underlying mechanism can be explained not just by a direct antitumor effect which is particularly important if the tumour is radiosensitive, but also by radiation-induced inhibition of osteoclast activity and stimulation of osteoblast activity. It follows that its role in skeletal metastases is not only limited to the palliation of pain but it is also oriented to prevent impending fractures and/or cord decompression in cases where vertebral metastatic lesions extend into the spinal canal or the nerve root exits. The initial antalgic effect can be reached in 24 hours and the maximum effect in 3-4 weeks after EBRT. A transitional increase of pain is possible in a sub-acute phase (Flare effect). In the case of cord compression, results of radiotherapy are closely linked to neurological status at time of treatment and patients who are already paraplegic, especially for over 48 hours, with loss of bladder control are unlikely to have neurological recovery with radiation [13]. All cases have to be urgently discussed within a multidisciplinary board in order to select those patients who will profit of an urgent surgical management. The Patchell's randomised phase III trial demonstrated that surgery plus postoperative radiotherapy was superior to radiotherapy alone in patients with metastatic spinal cord compression. Nevertheless, those cases need to be carefully selected according to well defined prognosticators, as histology, systemic disease extension and spinal metastasis extension are [14]. As far as fractionation schemes/doses for pain relief are concerned, international practice guidelines now support the assertion that Single Fraction (SF) radiation therapy is the standard of care for the relief of pain due to uncomplicated bone metastases [15]. Trials that have compared different SF doses showed that higher doses indeed produce superior response rates.

The most commonly administered SF dose is by far 8 Gy. This dose should be the standard due to its reproducible pain response and retreatment rates, and its safety profile. However, if the aim of radiotherapy also contemplates prevention of impending fractures via recalcification, a 30Gy/10fr scheme has been shown to have a significantly higher effect, especially in patients with breast or prostate histology. Prolonged fractionation is also associated with a longer duration of pain relief and should be considered in patients with a life expectancy (LE) above 6 months [16]. A growing problem, as metastatic patients live longer, is pain due to recurrence even in previously irradiated bone. A recent review of 70 full-text articles has shown an overall response to retreatment «aequo loco» of 68 % [17]. This is comparable to the overall response for first radiation. The authors found that a response to therapy is possible, even if the first irradiation failed. Data about an increased toxicity after a second irradiation couldn't be detected in this review in one part due to the fact that adverse events and toxicity are poorly reported due to the decreased ability to properly assess acute toxicity of re-irradiation. The international Bone Metastases Consensus Working Party recommends a 4-week waiting time before considering re-irradiation. In conclusion, the results of this meta-analysis allow to answer «YES» to the question of the effectiveness of re-irradiation on interdisciplinary tumorboards. Furthermore, the emergence of Stereotactic Body Radiotherapy (SBRT), essentially an extracranial extension of radiosurgery, has greatly enhanced the safety profile and effectiveness re-irradiation of bony metastases [18]. We therefore recommend SF 8 Gy to uncomplicated painful bone lesions in patients with unfavourable prognostic factors or LE < 6 months and longer schemes (30Gy/10fr or similar) in cases with LE ≥ 6 months. Re-irradiation should be considered in case of recurrence in previously irradiated volumes. Radiometabolic treatment with Radium 223 dichlorid has nowadays also an indication in the treatment in prostate cancer castration resistant patients with diffuse asintomatic bone metastases in absence of visceral involvement. In fact there has been a fase III study who has demonstrated an improvement of time to first symptomatic skeletal event in comparison to placebo and an improvement on overall survival [19].

Bisphosphonates and Denosumab

Patients with bone metastases have increased osteoclastic activity resulting in local bone destruction, this leads to pain, hypercalcaemia and skeletal related events (SRE) as pathological fractures and spinal compression, which significantly impact quality of life. Bone modifying agents, such as Bisphosphonates and Denosumab, inhibit the action of the osteoclasts and this leads to less bone loss and decrease of the risk of fractures.

Denosumab, an inhibitor of receptor activator of nuclear factor kappa-B (RANK) ligand, was superior to Zoledronic acid in many trials for bone metastases from solid tumors and it is generally well tolerated [20]. This fully human monoclonal IgG2 antibody is one of the best potential treatments for patients with bone metastases with the convenience of a subcutaneous injection and no requirement for renal monitoring (improved the time to the first and subsequent SREs when compared to Zoledronic acid) [20]. The recommended dose and schedule for Denosumab for the prevention of SREs is 120 mg every four weeks. Limitations are cost and/or reimbursement. The use of Denosumab is not approved in Multiple Myeloma at the moment.

The *Bisphosphonates* are analogs of pyrophosphate with affinity for hydroxyapatite, the principal bone mineral, and that prevent the dissolution of mineral bone and consequently prevent SREs. Particularly Zoledronic acid, given by 4 weekly intravenous infusion, seems to be the most efficacious Bisphosphonate, compared to Clodronate, Pamidronate, and Ibandronate (i.v. and oral), for reducing the risk of SREs in patients with breast or prostate cancer and with multiple myeloma [21]. A recent large randomized phase 3 trial showed that daily oral medication with Ibandronic acid 50 mg was inferior to monthly Zoledronic acid 4 mg in reducing SRE in patients with breast cancer but with the same acceptable side effects and less frequent renal toxic effects is another option in patients for whom the oral administration is preferable [22]. In a recent retrospective observational study in the USA Bisphophonates are reported as underutilized, especially in metastatic Prostate and Lung Cancer [23]. Previous analyses have shown that premature discontinuation of Zoledronic acid use was associated with higher monthly rates of skeletal complications [24].

Hypercalcemia is a common finding in metastatic malignancies. The local osteolysis due to metastases invasion of bone causes hypercalcemia (patients can have also hypercalcemia due to secreted factors, such as Parathyroid-related Hormone, or due to an excess of Vitamin D produced by malignancies). The mainstays of therapy are adequate intravenous saline infusion and Bisphosphonates administration [25].

Cementoplasty

Percutaneous procedures as Cementoplasty/Osteoplasty and Ablation techniques as Coblation, Cryoablation, Radiofrequency (RF), MicroWaves (MW), are possible alternatives, often used in association.

Vertebroplasty/Kyphoplasty (VP/KP) is a percutaneous interventional procedure established in early eighties by Galibert, Deramond et al. [26] for the radiological percutaneous treatment of aggressive vertebral hemangiomas. VP is a radiological procedure in which a needle is inserted into a vertebra under radiological guidance (CT and/or fluoroscopic); through this access coaxial devices can be used in order to obtain bioptic specimens and/or insert cement, usually Poly-Methyl MethAcrylate (PMMA), or specific instruments inside the vertebral lesion. The whole procedure is usually made in outpatients, in local anesthesia and intravenous sedation.

In selected Patients a ballon Kyphoplasty (KP) can be performed in order to obtain a non-surgical vertebral augmentation. Indications to VP and KP include: diagnosis (biopsy), pain palliation, stabilization, fracture arrest and/or prevention, debulking and local control. The prevalent goals are anyway pain control and bone stabilization. In patients with impending vertebral body collapse VP/KP may improve patient outcomes over simply waiting for the vertebral body to fracture [27]; the procedure is effective in reducing pain, add stability, and can be combined with radiotherapy or chemotherapy. VP/KP improve function and quality of life, decreases morbidity and mortality [28, 29] and can be considered «as a first-line treatment for painful myelomatous vertebral disease. More easily than surgery, VP and KP can be combined with radiotherapy» [30]. Many authors agree that a multimodality approach for the management of metastatic bone disease includes VP/KP procedures and the majority of patients will have excellent palliation with this approach [31]. The complication rate is low and usually little or with no importance; the most common are linked to some cement extravasation that can be paravertebral, inside the disc, epidural, intraforaminal, in adjacent veins. Very rare complications include: hemorrhage, infection, fracture (pedicle, ribs), pneumothorax, spinal cord or nerve root injury. Although the greatest number of bone lesions is extra-spinal (about 66%) osteoplasty beyond the spine (*Extra-Spinal Cementoplasty)* is not a very used procedure. Up to February 2013 the literature reported only 543 articles on this topic vs over 3000 about VP/KP. The procedure is very similar to VP/KP and has the same indications. As in VP/KP its complexity varies from very simple to complex depending on the site, shape and size of the lesions. The procedure can be associated to radiotherapy and to ablation procedures [32, 33, 34]. On the contrary of VP/KP extraspinal cementoplasty is less effective in consolidation in long bone since the lower resistance of cement to torsional stress (as in the diaphysis of long bones) in respect to pure axial stress (as in vertebrae and in flat bones) due to lower young module of PMMA in respect to normal bone [35]. Definitively, VP/KP and extra-spinal cementoplasty are safe and effective procedures in the palliative treatment of localized painful bone metastatic lesions, whose range of technical complexity is extremely wide.

Pain management

Pain is the most common symptom in patients with bone metastases. Metastatic extent does not directly correlate with the global pain burden perceived by the patients. According with daily clinical observations, some of them with advanced bone destruction do not report significant or only minimal pain. The gap between the radiologic bone architecture destruction and the effective clinical manifestations may be very surprising. Both osteolytic and osteoblastic metastases usually generate significant pain through different pathophysiological mechanisms including mechanical (loss of substance) and/or functional (loss of structure) pathways [1, 36]. Different pain clusters or syndromes can be produced by a sequential or concomitant arise of basis/background pain, spontaneous and movement-induced (incidental) pain. Episodical acute exacerbations of pain (breakthrough) represent a frequent constatation in clinical practice.

Available analgesic drugs can be considered as very efficacious in the management of cancer-related bone pain. In most cases, the right answer is a combination of different drugs targeting different pain mechanisms and pathways, like non-opioids, opioids and, very important in some particular settings, adjuvant analgesics [1, 37, 38]. According to the WHO-Guidelines [39] analgesic drugs should be administered «by the mouth», «by the clock» (following well-defined time intervals) and «by the ladder» (that means according to the levels of analgesic potency).

Non-opioid analgesic drugs like Paracetamol, Metamizol and *anti-inflammatory drugs* (like Diclofenac, Ibuprofen, Ketorolac, Celecoxib and others) may represent a good pharmacological basis but they are usually not enough if taken as a monotherapy [1, 36]. Anti-inflammatory drugs may rise some concerns in patients with a fragile condition, gastrointestinal and/or renal situation. *Corticosteroids* may have some indications (vertebral fracture, spinal cord compression), particularly for the pain management on the short term [40].

Opioids still represent the drugs of choice in moderate to severe malignant bone pain. According to the recent evidence, Morphine, Oxycodon or Hydromorphone can be alternatively used as first line-opioids [41]. The oral way should always be preferred whenever possible and the subcutaneous way should represent the first choice in patients

requiring parenteral drug administration where a venous access is not yet or no more available. Fears of long-term side effects or toxicities and/or addiction-related concerns are definitely not an issue of discussion in patients with short prognosis and should not prevent patients from receiving an adequate drug medication.

Endocrine- and chemotherapy

Palliative endocrine and chemotherapy may offer a contribution in the management of progressive metastatic bone involvement. In selected patients with advanced systemic disease, even though displaying rapidly declining performance status, a proper assessment of the potential risk-benefit of systemic therapies may help to identify patients who could potentially benefit from active treatments.

Surgery

Palliative surgery and osteosynthesis procedures may provide long-term or at least transient solutions in patients with pathological bone fracture. In many clinical situations surgery may help to restore mobility, functionality and to reduce or to control local or irradiating pain.

The indication for surgery in this setting should consider the general conditions of the patient, the estimated prognosis and, definitely, be a part of a multidisciplinary approach.

Conclusions

As we enter an era of outstanding progresses in cancer medicine, metastases-related bone problems and complications are and will remain complex clinical challenges. Their great prevalence forces medical oncologists and the whole medical community dealing with cancer patients to be alert and updated on this topic. Since the «multidisciplinary approach way» should be considered the currently best one if we look at the outcomes, an intensive collaboration is required from all the specialists to treat patients according to the evolving scientific knowledge. Some issues like proper assessment, accurate diagnostic procedures and adequate management still represent consolidated priorities.

Integrating active oncologic treatments, palliative surgery, supportive and palliative care concepts into the daily practice seems to be the way of the present and possibly even more, the way of the future.

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SAKK News

Annik Steiner, SAKK Coordinating Center, Bern

BOARD DECISIONS

At its annual board meeting and retreat on May 15 and 16, 2014, in Konolfingen, the SAKK Board accepted to conduct the following trials:

ETOP SPLENDOUR, coordinating investigator R. von Moos, Kantonsspital Graubünden. *Survival imProvement in Lung cancEr iNduced by DenOsUmab theRapy (SPLENDOUR). An ETOP sponsored / EORTC coordinated phase III trial in advanced NSCLC.*
The board agreed to participate in this international trial.

SAKK 06/14, coordinating investigator C. Rentsch, Universitätsspital Basel. *A phase I/II open label clinical trial assessing safety and efficacy of intravesical instillation of the recombinant BCG VPM1002 in patients with recurrent non-muscle invasive bladder cancer after standard BCG therapy.*
Notably, the use of BCG as a means of initiating anti-tumor immunity represents one of the most successful immunotherapies used in clinical practice. While successful, tumor recurrence and disease progression are seen often in these patients. VPM1002 is a genetically modified BCG vaccine for which preclinical studies have confirmed lower toxicity compared to conventional BCG. VPM1002 will be tested for safety, efficacy, tolerability and immunogenicity in a phase I/II clinical trial, respectively, in patients with tumor recurrence after a first BCG therapy. Of note, this will (to the best of knowledge) be the first in human trial with recombinant intravesical bacteria and the first in human intra-bladder application of VPM1002.

SAKK 09/14, coordinating investigator A. dal Pra, Inselspital Bern. *Dose intensified Salvage radiotherapy in combination with short-term enzalutamide after biochemical failure post-prostatectomy: a Phase I/II study.*
Enzalutamide is a promising agent to be employed in the management of earlier stages of prostate cancer. By addressing occult metastases and optimizing local control in patients with biochemical failure post-prostatectomy (~ 30 % of all surgical patients). The trial could substantially impact the treatment of this type of cancer which is the most common among men in Switzerland. It is hypothesized that dose intensified RT combined with a short-course of the second-generation anti-androgen, enzalutamide, is clinically beneficial in terms of progression-free survival and low toxicity profile in patients presenting biochemical failure post-RP. The board agreed to conduct this trial under the condition that the company supports the trial.

SAKK 96/12, coordinating investigators M. Joerger, Kantonsspital St.Gallen / L. Albiges, Institut Gustave Roussy, Villejuif (FRA). *Bone Turnover Markers in Patients Receiving 4-Weekly versus 12-Weekly Denosumab in the SAKK 96/12 Randomized-Non-Inferiority Phase III Trial. A Prospective Kinetic-Pharmacodynamic (K-PD) Population Modeling Analysis.*
This translational research sub-study of the trial SAKK 96/12 aims at investigating the prospective and predictive value of specific bone turnover markers and it enables an early first analysis of the safety and efficacy of the reduced treatment with denosumab in the main trial. The board agreed to conduct this translational research project.

SAKK 36/13, coordinating investigators U. Novak, Inselspital Bern / C. Renner, Onkozentrum Zürich *Combination of Ibrutinib and Bortezomib to treat mantle cell lymphomas patients – a multicenter phase I/II trial.*
The trial aims at investigating the combination of ibrutinib and bortezomib in mantle cell lymphoma. Both drugs are active in MCL and investigating the combination is very attractive. It is planned to perform the trial in cooperation with Italian and German organizations. The board agreed to conduct this trial under the condition that the company supports the trial.

SAKK 35/14, coordinating investigators E. Zucca, IOSI Bellinzona / E. Kimby, Karolinska University Hospital, Stockholm (SWE) / B. Ostenstad, Ullevål universitetssykehus, Oslo (NOR). *Extended Rituximab with or without Ibrutinib. A randomized blinded Phase II trial.*
SAKK has a long tradition in treatment of follicular lymphoma patients with «soft» treatment (i.e. without chemo

or radiation) based on rituximab solely or mainly. The aim of the trial is to study the activity and the safety of the 1st line treatment with ibrutinib in combination with RTX for patients with advanced follicular lymphoma in need of therapy. Furthermore, this trial would allow the search of new prognostic factors in gene expression and immunophenotyping. SAKK will collaborate with the Nordic Lymphoma Group in this trial. The board agreed to conduct this trial under the condition that the company supports the trial.

TRIANGLE, coordinating investigator U. Mey, Kantonsspital Graubünden. *Efficacy of Ibrutinib during R-CHOP/R-DHAP induction and after or in comparison to autologous stem cell transplantation (ASCT) in previously untreated patients with mantle cell lymphoma.*
This trial was designed by the European Mantle Cell Lymphoma Network. It is an important trial in this disease and would allow Switzerland to be integrated in the European setting. The board agreed to participate in the trial.

SAKK 16/14, coordinating investigator S. Rothschild, Universitätsspital Basel. *Perioperative anti-PD-L1 antibody MPDL3280A in addition to standard neoadjuvant chemotherapy in non-small cell lung cancer (NSCLC) patients with mediastinal lymph node metastases (stage IIIA, N2).*
The hypothesis of the trial is that the addition of preoperative immunotherapy (anti-PD-L1 antibody) to standard chemotherapy (cisplatin/docetaxel) could improve local control, event-free survival and overall survival in stage IIIA (N2) NSCLC. The addition of the anti-PD-L1 antibody offers a novel approach as the outcome of patients with stage IIIA NSCLC is poor. The task is to substantially decrease the number of patients who die in spite of intensive multimodality treatment. The addition of this novel treatment modality (immunotherapy) has the potential to improve the outcome without adding additional substantial toxicity. The board agreed to conduct this trial under the condition that the company supports the trial.

BIG 6-13, coordinating investigator U. Novak, Inselspital Bern. *A randomised, double-blind, parallel group, placebo-controlled multi-centre Phase III study to assess the efficacy and safety of olaparib vs placebo as adjuvant treatment in patients with high risk germline BRCA mutated HER2negative breast cancer who have completed definitive local and systemic neoadjuvant/adjuvant treatment.*
This is an international trial in a niche indication by the Breast International Group. The board agreed to participate in the trial.

Revised regulations on competences and signatures
The executive board has revised the regulation on competences and signatures. The revision mainly gives the project managers more competences. The Board members approved of the changes.

Approval of the president of the project group lung cancer
In their last meeting, the project group lung cancer appointed *Oliver Gautschi* for a second term as president. The Board members approved of this election.

AWARDS AND PROMOTIONS

Florian Strasser, senior physician oncology and palliative medicine at the Kantonsspital St.Gallen, is new chair of the Working Group Palliative Care of the European Society of Medical Oncology (ESMO) since the beginning of this year.


Florian Strasser

Matthias Guckenberger was appointed full professor and director of radio-oncology at the University Hospital Zürich. He joined the SAKK Project Group Lung Cancer.


Matthias Guckenberger

GENERAL ASSEMBLY

During the General Assembly, which took place on June 26, the participants reelected *Walter Marti* from the Kantonsspital Aarau and *Arnaud Roth* from the University Hospital Geneva as Board members.

The members of the General Assembly were informed about the implementation of the new Human Research Act. The implementation of the new law without a transition phase was very challenging for all stakeholders and resulted in significant delays for trial/amendment authorization.

Furthermore, the General Assembly discussed the possibilities of involving the voices of patients and patient organizations in the research of SAKK in the future.

Additionally, the General Assembly approved to accept the renewed mandate from the scientific committee HSM and to keep playing an active part in elaborating recommendations how the treatment of rare cancers should be organized in the future.

SEMI-ANNUAL MEETING

On June 26 and 27, SAKK held its summer semi-annual meeting in Bern, which was attended by more than 250 specialists.

Gateway/RTF-CCR/SAKK Research Grant: Winning trial awarded

Award winner Radek Skoda (right) with Shawn Stephenson, President Rising Tide Foundation.

Shawn Stephenson, Chairman and *Eveline Mumenthaler*, Director Rising Tide Foundation, along with *Teresa Hall Bartels*, President of Gateway for Cancer Research, awarded the winner of the Gateway/RTF-CCR/SAKK Research Grant 2014, Prof. Dr. *Radek Skoda* from the University Hospital Basel, for a novel «Phase II study to test the effects of beta-3-sympathicomimetic agonists on the disease course and mutant allele burden in patients with myeloproliferative neoplasms (MPN)». The winning proposal was chosen out of 10 initial grant applications and stood out for its high potential for patient benefit, significance, innovation and feasibility.

With no current cure available, MPN are a group of chronic leukemias (blood cancers) in which patients produce too many blood cells. These increased blood cell numbers cause problems to the patient such as bleedings or thrombosis and some patients may progress to acute leukemia, a life threatening condition. Most MPN patients (>80% overall) have a gene mutation called JAK2-V617F. The disease is maintained by mutant MPN stem cells that reside in the bone marrow in specialized locations called «niches». These niches need connections to the nervous system. New findings show that these connections are destroyed by the presence of the mutated MPN stem cells. The research teams around the co-applicant Prof. *Simon Mendez-Ferrer* and Prof. *Radek Skoda* found that some drugs (beta3-sympathicomimetics) can restore these damaged niches and at the same time reduce the MPN disease manifestation in a mouse model of MPN. Such sympathicomimetic drugs are already being used to treat patients with asthma or hyperactive bladder. These drugs have shown to have only few side effects.

The research team is to test the effects of the beta-3-sympathicomimetic drug Mirabegron (Betmiga®) in 36 patients with MPN that carry a JAK2-V617F mutation. Betmiga® is currently approved for the treatment of hyperactive bladder. The researchers expect that Mirabegron will have a beneficial effect on bone marrow niche cells and will thereby improve the disease manifestation in MPN patients. This study should provide a rapid answer whether targeting the nervous system of the niche cells could be useful for patients with MPN and warrants to be tested in larger and more long-term studies.

There is currently no cure for MPN. The approach proposed by Prof. *Skoda* and his team is novel and fundamentally different from the current strategies, since the primary target of therapy is the correction of the stem cell niche damage, rather than the malignant clone itself.

The Gateway/RTF-CCR/SAKK Research Grant for outstanding and novel clinical cancer research is endowed for 450 000 U.S. dollars and is jointly awarded by Gateway for Cancer Research, a U.S.-based non-profit organization, the Rising Tide Foundation for Clinical Cancer Research, a Swiss-based foundation, and SAKK. As a joint front, Gateway, RTF-CCR and SAKK decided in 2011 to create a strategic partnership with the aim to stimulate innovative and practice relevant oncology research that may lead to more potent, less toxic and potentially life-saving treatment options for cancer patients. The Call for Proposals was now

Shawn Stephenson, RTF Chairman; Morgan Stephenson, RTF; Eveline Mumenthaler, RTF, Director; Beat Thürlimann, SAKK President; Jakob Passweg, University Hospital Basel; Teresa Hall Bartels, Gateway for Cancer Research, President; Radek Skoda, University Hospital Basel; Wendelin Zellmayer, Rising Tide, CEO; Hermann Schulin, RTF, Board Member; Peter Brauchli, SAKK CEO (f.l.t.r.)

conducted for the second time. All submitted proposals were reviewed by an international review committee comprising of Gateway, RTF-CCR and SAKK scientists in a two-step procedure, with a final decision in May 2014.

Additional to the Gateway/RTF-CCR/SAKK Research Grant 2014, Gateway for Cancer Research stepped up and agreed to fund also the runner-up of the proposals, the grant application by *Christoph Mamot* from the Kantonsspital Aarau with the title «multi-center, investigator-initiated single arm phase II trial to evaluate the efficacy of anti-EGFR immunoliposomes in patients with pretreated triple-negative breast cancer». The Scientific Review Committee was impressed with this proposal and the high potential for patient impact.

SAKK/Dr. Paul Janssen Fellowship for Benjamin Kasenda

Benjamin Kasenda from the University Hospital Basel obtained the SAKK/Dr. Paul Janssen Fellowship, which is jointly awarded by SAKK and Janssen-Cilag. The educational grant is endowed with CHF 50 000.- and is aimed at offering young doctors the opportunity to spend four months at a renowned research center abroad to gain experience and acquire the necessary know-how and tools to develop and conduct top-quality clinical trials.
Kasenda spends his fellowship at the Royal Marsden Hospital in London where he manages a project in the field of kidney cancer. For this rare entity, new agents have been developed over the last years, however research on prognostic factors or side effects is still rare. In *Kasenda's* view this opportunity to work and conduct clinical research at this large UK oncology centre offers a great chance to broaden his clinical and research experiences as an oncologist in training.

SAKK President Beat Thürlimann, Award winner Benjamin Kasenda and Sabine Albrecht, Janssen-Cilag

PRESENTATIONS Q2 2014

Abstracts
ASCO Annual Meeting 2014

Poster
Templeton A. et al. **Prevention of symptomatic skeletal events with denosumab administered every 4 weeks versus every 12 weeks – a non-inferiority phase III trial (SAKK 96/12, REDUSE).**

Koeberle D. et al. **Sorafenib with or without everolimus in patients with unresectable hepatocellular carcinoma (HCC): A randomized multicenter phase II trial (SAKK 77/08 and SASL 29).**

Poster discussion
Von Moos R. et al. **Neoadjuvant radiotherapy (RT) combined with capecitabine (Cape) and sorafenib (Sor) in patients (pts) with locally advanced, k-ras-mutated rectal cancer (LARC): A phase I/II trial SAKK 41/08.**

Rochlitz C. et al. **SAKK 24/09: Safety and tolerability of bevacizumab plus Paclitaxel vs. bevacizumab plus metronomic cyclophosphamide and capecitabine as first-line therapy in patients with HER2-negative advanced stage breast cancer. A multicenter, randomized phase III trial.**

Oral presentation
Sargent DJ. et al. **Prognostic impact of deficient mismatch repair (dMMR) in 7,803 stage II/III colon cancer (CC) patients (pts): A pooled individual pt data analysis of 17 adjuvant trials in the ACCENT database (SAKK 60/00).**

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Lung Cancers

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Joerger M, Baty F, Früh M, Droege C, Stahel RA, Bettticher DC, von Moos R, Ochsenbein A, Pless M, Gautschi O, Rothschild S, Brauchli P, Klingbiel D, Zappa F, Brutsche M. **Circulating microRNA profiling in patients with advanced non-squamous NSCLC receiving bevacizumab/erlotinib followed by platinum-based chemotherapy at progression (SAKK 19/05).** *Lung Cancer. 2014 May 29.*

Breast Cancers

SAKK 92/08
Templeton AJ, Ribi K, Surber C, Sun H, Hsu Schmitz SF, Beyeler M, Dietrich D, Borner M, Winkler A, Müller A, von Rohr L, Winterhalder RC, Rochlitz C, von Moos R, Zaman K, Thürlimann BJ, Ruhstaller T; Swiss Group for Clinical Cancer Research (SAKK) Coordinating Center. **Prevention of palmar-plantar erythrodysesthesia with an antiperspirant in breast cancer patients treated with pegylated liposomal doxorubicin (SAKK 92/08).** *Breast. 2014 Mar 19.*

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Bonnefoi H, Litière S, Piccart M, Macgrogan G, Fumoleau P, Brain E, Petit T, Rouanet P, Jassem J, Moldovan C, Bodmer A, Zaman K, Cufer T, Campone M, Luporsi E, Malmström P, Werutsky G, Bogaerts J, Bergh J, Cameron DA; on behalf of the EORTC 10994/BIG 1-00 Study investigators. **Pathological complete response after neoadjuvant chemotherapy is an independent predictive factor irrespective of simplified breast cancer intrinsic subtypes: a landmark and two-step approach analyses from the EORTC 10994/BIG 1-00 phase III trial.** *Ann Oncol. 2014 Mar 11.*

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Cuzick J, Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, Saunders C, Roche N, Mansel RE, von Minckwitz G, Bonanni B, Palva T, Howell A; IBIS-II investigators. **Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial.** *Lancet. 2014 Mar 22.*

Leukemia

CML III
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Gastrointestinal Cancer

SAKK 44/00
Bernhard J, Dietrich D, Glimelius B, Bodoky G, Scheithauer W, Herrmann R. **Clinical benefit response in pancreatic cancer trials revisited.** *Oncol Res Treat. 2014 Jan 20.*

Palliative Care

SAKK 95/06
Blum D, Rosa D, deWolf-Linder S, Hayoz S, Ribi K, Koeberle D, Strasser F. **Development and Validation of a Medical Chart Review Checklist for Symptom Management Performance of Oncologists in the Routine Care of Patients With Advanced Cancer.** *J Pain Symptom Manage. 2014 May 23.*

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Matter-Walstra K, Klingbiel D, Szucs T, Pestalozzi BC, Schwenkglenks M. **Using the EuroQol EQ-5D in Swiss Cancer Patients, Which Value Set Should be Applied?** *Pharmacoeconomics. 2014 Mar 27.*

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Matter-Walstra KW, Achermann R, Rapold R, Klingbiel D, Bordoni A, Dehler S, Jundt G, Konzelmann I, Clough-Gorr KM, Szucs T, Schwenkglenks M, Pestalozzi BC. **Delivery of health care at the end of life in cancer patients of four swiss cantons a retrospective database study (SAKK 89/09).** *BMC Cancer. 2014 May 1.*

Consultancy
Cathomas R, Klingbiel D, Geldart TR, Mead GM, Ellis S, Wheater M, Simmonds P, Nagaraj N, von Moos R, Fehr M. **Relevant risk of Carboplatin underdosing in cancer patients with normal renal function using estimated GFR: Lessons from a stage I Seminoma cohort.** *Ann Oncol. 2014 Mar 25.*

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Fehr M, Geldart T, Klingbiel D, Cathomas R. **Measurement or estimation of glomerular filtration rate in seminoma patients: Quite another cup of tea.** *Eur J Cancer. 2014 Jun 7.*

SAKK DATES 2014

October 21	Board Meeting
October 23&30	Investigators' Education
November 19	General Assembly
November 20&21	Semi-Annual Meeting

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Law for cancer registration

Every year in Switzerland, 37 000 people are diagnosed with cancer and nearly 16 000 affected individuals die.

In March 2013, the federal government launched the initiative for a law for cancer registration with the aim to improve the overall minimal data on cancer in Switzerland. Main emphasis of the registration is to obtain profound evidence on cancer prevention programs, better proofs of the effectiveness of cancer diagnosis and treatments and an improved planning for the infrastructure of medical care. Moreover, the enhanced data sets may hopefully allow a faster evaluation of Swiss-wide data with higher quality. It is also intended that anonymized data shall be accessible for researchers and governmental administration as well as for statistics and extended investigations. This may also foster research in areas like epidemiology, quality of life, rare cancers, long-time implications of treatments and others.

The new law shall determine which minimal data on the diagnosis, treatment and follow-up must be collected nationwide, and what data may be gathered for specific research questions such as treatment success, further development of the disease or quality of life. Furthermore, a suitable process to access collected data for researchers has to be defined. For both questions, national institutions like the National Institute for Cancer Epidemiology and Registration (NICER), the Swiss Paediatric Oncology Group (SPOG), Children's Cancer Registry and SAKK have been involved in this process. While NICER was actively involved in the determination of the minimal data set, SAKK was asked for advice how to regulate access to patient data for recruitment into clinical trials and research through the cancer registration. SAKK gave, in alignment with SPOG, the Children's Cancer Registry and a cantonal cancer registry an extended answer to this question. Also NICER is preparing a profound report by the end of June, defining the minimal data set that is necessary to give the answers to the asked questions and questions that may be asked in the future. NICER will include also the experiences from other European countries that have introduced such registrations a decade ago. The Federal Office of Public Health (FOPH) has now to finalize a law that balances well the practicability and research on one hand and the sensitivity of patient data and patient integrity on the other hand. The draft of the law is likely to be presented to the parliament this fall.

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Paediatric Oncology in Switzerland: Infrastructure and Results

J. R. Rischewski, Head of the Structural Development Working Group (SDWG) of the Swiss Paediatric Oncology Group (SPOG)

Introduction

The Swiss Paediatric Oncology Group (SPOG), one of 16 national paediatric haematology and oncology societies in Europe (11), decided in 2013 to formalize already existing and functional efforts of the group to ensure, maintain and improve the quality of paediatric oncologic health care in Switzerland. SPOG therefor established a Structural Development Working Group (SDWG) to analyse structural and quality aspects of paediatric oncological supply in Switzerland. In a first step towards quality measurement, a survey of the infrastructure of the 9 SPOG Paediatric Cancer Centres (PCC) (Aarau (A), Basel (B), Bellinzona (Bel), Berne (Be), Geneva (G), Lausanne (L), Lucerne (Lu), St. Gallen (S) and Zurich (Z)) was initiated.

We also compared published overall survival data (OS) of paediatric cancer patients in Switzerland and other European Countries, in order to document what could so far be gained by the existing structures.

Method

The American Society of Pediatrics has published infrastructural requirements for paediatric oncologic units in the USA (1). Despite the fact that health care structures are different, we used these requirements as a template to record the resources of the 9 SPOG centres. The centres self-reported within the templates between October and December 2013, and sent it to the SPOG for summary.

The centres also self-reported patient load as sum of three years (2010-2012), and the available number of specialists (paediatric haemato-oncologists) who took care of the patients. A ratio of diagnoses per specialist per year was calculated.

All patients with a first diagnosis of a malignant disease according to ICCR-3 (13), relapse or secondary tumor were counted, patients with Langerhans cell histiocytosis and aplastic anemia were also included.

To describe OS of malignant diseases in children in Switzerland the actual numbers as published by the Swiss Childhood Cancer Registry Annual report were used (2).

To compare OS in Switzerland to other European countries, the recent figures published by Gatta (3) were used, which assessed regional and national cancer and death registries in Switzerland and in Europe to produce their findings.

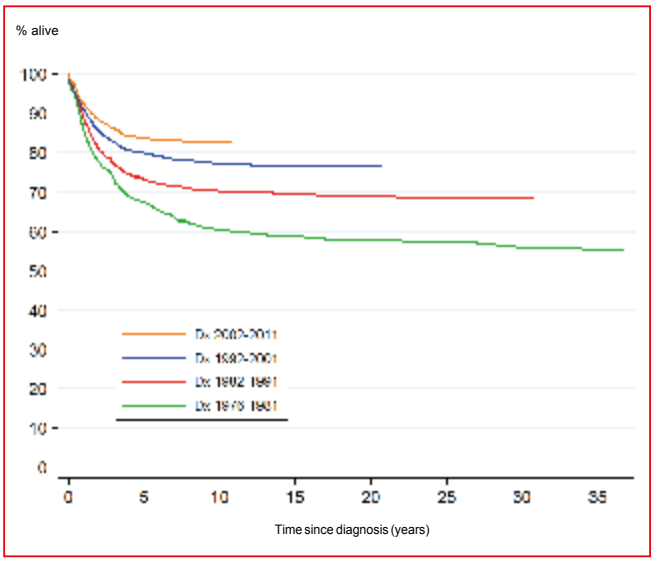

Figure 1: Survival of patients in the SCCR, by period of diagnosis. Swiss residents; age at diagnosis 0-14 years; period of diagnosis 1976-2011; all diagnoses (ICCC-3 or Langerhans cell histiocytosis); N=5913; adjusted for sex, age at diagnosis and ICCC-3 groups. The graph shows an actuarial curve presenting overall survival up to 35 years after diagnosis for patients diagnosed between 1976 and 2011, grouped in four periods. In total, 1503 (25%) children have died. Ten-year survival increased from 60.5% in children diagnosed between 1976 and 1981, 70.3% in children diagnosed between 1982-1991, to 77.3% in children diagnosed between 1992 and 2001, and reached 82.7% in children diagnosed within the last decade. Graph taken with permission from (2).

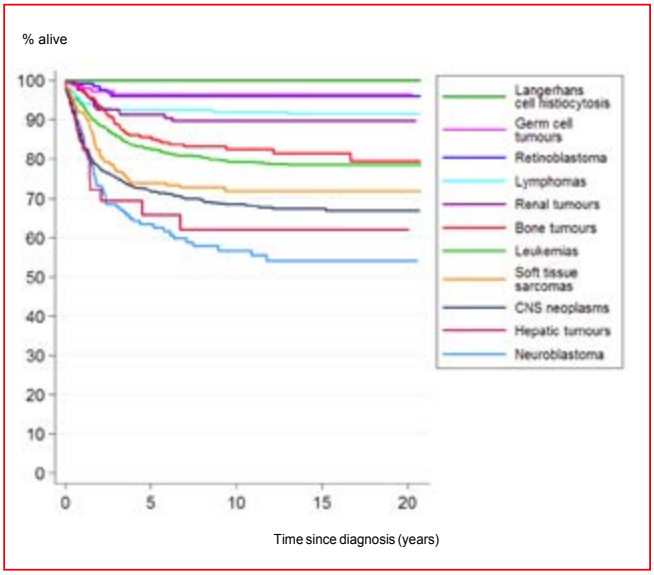

Figure 2: Survival of patients by diagnostic groups according to ICCC-3. Swiss residents; age at diagnosis 0-14 years; period of diagnosis 1992-2011; all diagnoses (ICCC-3 or Langerhans cell histiocytosis); N=3822; adjusted for sex and age at diagnosis. The graph presents survival by diagnostic group according to ICCC-3 in cases diagnosed between 1992 and 2011. Of these, 756 (19.8%) have died. The following numbers describe five-year survival for each main diagnostic group: 82.6% for cases with leukaemias; 92.4% for those with lymphomas; 71.7% for central nervous system neoplasms; 63.4% for neuroblastoma; 96.1% for retinoblastoma; 91.3% for renal tumours; 65.7% for hepatic tumours; 85.6% for malignant bone tumours; 74.0% for soft tissue sarcomas; 96.4% for germ cell tumours; and 100.0% in Langerhans cell histiocytosis. Graph taken with permission from (2).

The International Classification of Childhood Cancer (ICCC-3) distinguishes 12 groups of cancers. The most common are leukaemias (33% of all cancers), followed by tumours of the central nervous system (20%; especially brain tumours); and lymphomas (13%). Other cancers arise from embryonic tissue. These include neuroblastoma (7%) from primitive neural tissue, nephroblastoma (5%) from renal tissue, hepatoblastoma (1%) in the liver, retinoblastoma (3%) from cells of the retina, as well as germ cell tumours (3%). The latter may arise in the gonads (ovaries and testes), or in other sites, for example in the brain (intracranial germ cell tumours). In older children, malignant bone tumours (4%) and soft tissue sarcomas (7%), which arise from abnormal connective tissue, are occurring with increasing frequency. Sometimes children also develop melanomas and other rare tumours (3%). Langerhans cell histiocytosis (3%) is not encoded as malignant disease according to ICCR-3, but is also reported to Swiss Childhood Cancer Registry (SCCR). (2)

Results

All 9 SPOG centres replied to the questionnaire. Infrastructural details correspond to the state at the end of 2013. The results are summarized in table 1 and 2.

None of the Swiss centers fulfill all the requirements from the American Society of Paediatrics. Seven of the nine SPOG centres reported only minor infrastructural differences, apart from the restriction of allogenic stem cell transplantation to three centres. Transition times for requirements not available in a PCC on the children's hospital compound are between five and 150 minutes. The actual patient load for all centers together was 345 patients per year. The smallest center cared for 4% of the patients, the largest for 27%, the remaining for 5-19% each of the patients. The specialist/patient per year ratio varied between 5.2 and 22.

OS in Switzerland as reported by the SCCR are displayed in figure 1 and 2, and in italics in table 3. OS in other European countries as reported by Gatta (3) are summarized in table 3. The table displays figures generated by differing epidemiological methods, please refer to the original publication for full details.

Discussion

15% of the Swiss population are below 15 years of age, corresponding in 2012 roughly to 1.200.000 children (10). Around 11% of the patients reported to the Swiss Childhood Cancer Registry (SCCR) are non Swiss residents (2). The nine SPOG centers cared for 345 new patients/year between 2010 and 2012.

Published 5yOS rates for all paediatric cancers in Switzerland are at least at the level of the Central European EUROCARE-5 data (table 3). The European and Central European rates have been reported by Gatta (3) to be significantly above Eastern European rates. The Swiss 5yOS figures for the disease subgroups do also fit well into the range of the Central European EUROCARE-5 data. EUROCARE-5 evaluated the OS in 28 European countries. 5yOS in Switzerland was in the upper 25% for acute lymphoblastic leukemia, and second for 5yOS for all cancers combined (CNS tumors excluded in Gatta's analysis). Disparities between countries and regions in 5yOS ranged from 70% to 82%. For neuroblastoma a further evaluation of the Swiss 5yOS data is necessary, the published data do not allow for an interpretation of the apparent worse outcome in Switzerland in comparison to the Central European figures. It may be a result of an underreporting of surgically only managed patients with excellent prognosis, however, this remains to be proven. For leukemia, lymphoma, osteosarcoma, Ewing sarcoma and

Personnel	available off site, transition time in minutes	not available
Board certified paediatric hemato/ oncologist, FMH		
365/24 on call paediatric hemato/ oncologist service		
Specialised oncologic nursing team (experience > 2 years)		
Board certified paediatric radiologist, FMH		Bel (1)
Board certified paediatric surgeon, FMH		
Board certified paediatric neurosurgeon, title from a neurosurgical society		A, B, Be, Bel, G, L, S, Z (2)
Neurosurgeon with paediatric experience	S 5, Z 10	Bel
Urology with paediatric experience		
Orthopaedic surgeon with paediatric experience	Z 15	
Opthalmological surgeon with paediatric experience	B 10, S 5, Z 10	Bel
ENT surgeon with paediatric experience	B 10, S 5	
Dentist with paediatric experience	B 10	
Gynecologist with paediatric experience	B 10	
Radiation Oncologist with paediatric experience	B 10, S 5, Z 10	
Pathologist with special experience in paediatric malignancies	S 5, Z 10	
Paediatric subspecialities:		
- anaesthesiology		A (1)
- intensive care		A, Bel
- infectious diseases		Bel
- cardiology		
- neurology		
- endocrinology		
- genetics		
- gastroenterology		
- psychiatry		
- nephrology		A
- pulmonology		
physical and mental rehabilitation		
social worker		
psychologist		
family support group services		Bel
paediatric nutrition expert		
Facilities		
Intensive care unit, immediately accessible, fully staffed		A (3)
CT		
MRI	S 5	
PET	B 10, S 5, Z 10	
Radionuclid imaging	B 10, S 5, Z 10	
ultrasound		
angiography	B 10, Z 10	
paediatric equipped radiation therapy (for all centers proton therapy available at PSI (4))	B 10, S 5, Z 10	
flow cytometry	B 10, S 5	

→

Table 1. Infrastructure of the 9 SPOG Paediatric Cancer Centres (PCC) (Aarau (A), Basel (B), Bellinzona (Bel), Bern (Be), Geneva (G), Lausanne (L), Lucerne (Lu), St. Gallen (S) and Zurich (Z)). Base of the questionnaire are the infrastructural requirements for pediatric oncologic units in the US. As published from the American Society of Pediatrics (1). Available off site means not available in the hospital compound containing the children's hospital. Transition times are transport times in an ambulance car. If a centre is not named in a line, the requirement is fulfilled.

Personnel	available off site, transition time in minutes	not available
immunochemistry	B 10	
access to Cytogenetics	B 10	
access to hemodialysis/ hemofiltration (infant)	A 30, B 55, Bel 150, Lu 45, S 70	
access to apheresis for collection and storage of hematopoietic progenitors	A 30, B 10, Bel 150, Be 55 (5), L 40, Lu 45, S 70	
Capabilities		
chemistry lab able to monitor drug levels		
blood bank		
pharmacy		
isolation rooms from airborne pathogens, specify:		
- HEPA filtration		A
- laminar flow		A
- positive/negative pressure rooms		A
access to stem cell transplantation	A 30, Bel 150, Be 55 (5), L 40, Lu 45, S 70	
educational and training programs		
coordination of services (eg home health, palliative care)		
regularly held multidisciplinary tumor board(s) (6)		
follow up program		
SPOG membership		
education for patients, caregivers, parents		
translation services full time available		
quality assessment programs ongoing		Bel
formal programs for cancer education for the family and self management		Bel

1. 24/7 staff with pediatric diagnostic experience present
2. Position filled in 2014
3. Adult unit on site
4. Paul Scherrer Institut, CH-5232 Villigen
5. Autologous available on site
6. A, Bel and Lu are also regular members of specialized Tumorboards in B and/or Z

soft tissue tumours, further subgroup analyses of the Swiss data are needed to allow for more exact comparisons. The total patient numbers are too small for single center 5yOS comparisons within Switzerland.
In summary, published figures show that 5yOS in Switzerland is within the highest range reported in Europe.

The reported physician staffing for oncological needs is within the recommended range as reported by Halton (12) for the Canadian healthcare system, proposing an oncologist ratio of 1/15 patients. As the Swiss paediatric hemato-oncologists also cover the hematological needs of the patients, and Halton recommended 1 hematologist per 2.5 oncologists, at least half of the centres would have a need for more physicians. However, whether these figures apply to the Swiss healthcare system remains to be proven. Individual infrastructural differences of the PCC's, like the number of assigned non specialists to the care of the patients as well as non hemato-oncological duties of the specialists may explain in part the differences in staffing in the PCC's.

None of the Swiss PCC's fulfilled all the requirements from the American Society of Paediatrics. Seven of the nine SPOG centers reported only minor infrastructural differences, apart from the restriction of allogenic stem cell transplantation to three centres. Transition times for requirements not available in a PCC on the children's hospital compound are between five and 150 minutes. In relation to the excellent 5yOS rates the nine PCC's, their infrastructure and cooperations guarantee good outcome combined with a chance for adequate quality of life through treatment close to home and family.

Table 2. Percentage of specialist positions in the PCC's, separated for haematopoietic stem cell transplantation duties and without. The figures in brackets represent diagnoses/specialist/year or transplantations/specialist/year.

Center	% positions Ped. Hemato-/Oncologist, board certified		number of diagnoses (a), sum of 2010,2 011, 2012 and (in brackets) number of diagnoses/specialist/year	stem cell transplant pts. < 18 ys, sum of 2010, 2011, 2012 and (in bracket s) number of transplantations/specialist/year	
	transplant excluded	transplant only		allogenic	autologous
Aarau	160% (b)		**56** (11.7)		
Basel	400%	100%	**62** (5.2)	11 (3.7)	6
Bern	500%		**143** (9.5)		22
Bellinzona	120%		**37** (10.3)		
Geneva	300%	100% (c)	**107** (11.9)	13 (4.3)	1
Lausanne	300%		**201** (22) (d)		
Lucerne	250%		**90** (12)		
St Gallen	280%		**62** (7.4)	7 (e)	2 (e)
Zurich	600%	200%	**276** (15.3)	62 (10.3)	6

a. all first diagnoses, relapses, secondary tumours, including HLH and aplastic anemia, stem cell transplant patients excluded
b. increased to 250% in 2014
c. increased to 150% in 2014
d. HLH and aplastic anemia not reported
e. performed at adult site

		Europe	Central Europe	CH	Eastern Europe
	crude incidence rate for malignant cancers 2000-2006 (per 100000/year)	13.4	13.7	12.7 *16.2*	12.0
% 5 year survival	all cancers 2005-2007	79.1	81.0	87 *82.7*	70.2
	acute lymphoid leukemia	87.6	90.1	*82.6*	80.3
	acute myeloid leukemia	64.4	67.3		49.0
	Hodgkin's lymphoma	95.7	96.8	*92.4*	90.6
	non-Hodgkin lymphoma (d)	85.1	86.5		78.3
	Burkitt's lymphoma	93.1	94.3		84.8
	all CNS cancers	58.2	56.6	*71.7* (a)	54.5
	neuroblastoma	69.0	70.3	*63.4*	61.6
	Wilms tumor	89.8	94.4	*91.3* (b)	83.9
	osteosarcoma	64.3	70.5	*85.6*	64.3
	Ewing's sarcoma	66.6	69.5		46.2
	rhabdomyosarcoma	68.5	76.1	*74.0* (c)	39.3
	retinoblastoma	97.9	98.7	*96.1*	81.0

Table 3. Overall Survival figures as reported by Gatta et al (3) in EUROCARE-5 in comparison to figures from the *Swiss Childhood Cancer Registry* (SCCR) (in italic) as reported in 2012 (2). The figures from the SCCR represent partially other cohorts: (a) = all CNS tumors, (b) = all renal cancers, (c) = all soft tissue sarcoma. (d) = (except Burkitt's lymphoma). The figures are not completely comparable due to differences in the reported disease categories, and due to different methods of data catchment. Published 5yOS rates for all paediatric cancers in Switzerland are above the all European and the Central European rates. The European rates have been reported by Gatta to be significantly above the Eastern European rates. The Swiss 5yOS figures for the disease subgroups do fit well into the Central European EUROCARE-5 data. EUROCARE-5 evaluated the OS in 28 European countries. 5yOS in Switzerland was in the upper 25% for acute lymphoblastic leukemia, and second for 5yOS for all cancers combined (CNS tumors excluded).

Measuring, maintaining and improving the quality and structure of healthcare for rare diseases is an important, complex and scientifically challenging task.
The excellent 5yOS rates for all paediatric cancers in Switzerland reflect the high quality of the health care for children with cancer in Switzerland. The evidence for outcome improvement by further patient concentration in paediatric oncology, especially for surgical procedures is not conclusive, apart from the accepted necessity to include as many patients as possible in therapy optimization studies, and the need for a to be defined minimum standard of available ressources (6,7,8,9).

We therefor conclude, that the existing structures to care for paediatric oncologic patients in Switzerland should be modified with great care and in a strictly evidence based process in order not to compromise the good OS results (especially within the context of the intercantonal agreement for HSM [IV-HSM]) (4,5)). Continuous improvement and intensification of collaborations between the centers is certainly in the interest of our patients. SPOG therefor decided to intensify the existing networking between the PCC's e.g. by common tumour boards within three network regions, instead of concentrating patients on fewer centres. This strategy strengthens the quality of management (every individual patient is reviewed by several specialists) without compromising a close to home patient management.

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Trends in survival from oesophageal cancer in Switzerland

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Introduction

Oesophageal carcinoma is a relatively rare disease with a dismal prognosis. During 2007-2011 about 11 in 100'000 men (or 392 in total) and about 4 in 100'000 women (128 in total) were diagnosed each year with oesophageal cancer, while the yearly death toll due to the disease was 9 in 100'000 men (327 in total) and 3 in 100'000 women (106 in total) [1]. Age-adjusted incidences rates for cancer of the oesophagus have been increasing in Switzerland for both sexes since the beginning of cancer registration in the late Seventies and early Eighties of the 20th Century, with recent signs of levelling off, while mortality rates are steadily declining in men, but remaining stable in women [1]. Disease risk is considerably higher in men and moderately higher in the French- or Italian-speaking part of Switzerland. Both, the sex-specific and the region-specific age-adjusted risk ratios have declined over time from initially 5.0 to 3.8 for men versus women and from 2.0 to 1.4 for French-/Italian- versus German-speaking region, respectively.

In the present descriptive study, epidemiological information from tumour registries of seventeen Swiss cantons have been collapsed to examine the survival patterns of patients diagnosed with malignant primary cancer of the oesophagus during the last 30 years.

Methods

This study is based on the National Core Dataset (NCD) managed by the National Institute for Cancer Epidemiology and Registration (NICER) for the purpose of national cancer monitoring in Switzerland. Twenty of 26 Swiss cantons have transmitted population-based cancer data to the NCD up to diagnosis date 31.12.2011. Cancer cases from 17 cantons were collapsed for this report: Appenzell Ausserrhoden (AR) and Appenzell Innerrhoden (AI), Basel-Landschaft (BL) and Basel-Stadt (BS), Fribourg (FR), Geneva (GE), Glarus (GL), Graubünden (GR), Lucerne (LU), Nidwalden (NW), Obwalden (OW), St. Gallen (SG), Ticino (TI), Uri (UR), Valais (VS), Zug (ZG) and Zurich (ZH). The cantons of Neuchâtel, Jura and Vaud could not be included, because they do not provide information on patient survival to the NCD.

Cancer registries recorded all incident cancer cases diagnosed in their resident population and assessed cases' survival by active and/or passive follow-up until 31.12.2011. We extracted 5'519 malignant primary cancer diagnoses for oesophagus (ICD-10 C15) from 1980 to 2011. For the cantons BL and BS the latest available year of diagnosis was 2009. We excluded all cases diagnosed at death (N=86) or with a death certificate as the only source of information (N=107). Case finding via death certificates was infrequent (3%-7%, depending on cancer registry). Patients with multiple primary tumours (22%) were included [2]. Excluded were 78 cases because no active follow-up has been performed. Recent active follow-up was lacking for 133 cases (i.e. follow-up <2011). The vital status of these cases was set lost to follow-up using the date of last contact. A total of 5'248 cases (95%) remained for analysis, with 86% of observations uncensored (i.e. patients who have died).

Because we did not assume survival up to 31.12.2011 in the absence of reported death (i.e. based on passive follow-up alone), our survival estimates will be conservative. Using the assumption of survival in the absence of reported death could overestimate survival because two large registries did not utilize death certificates for several diagnosis years: ZH (1980-1996) and BS/BL (1981-2001, 2008-9).

Completeness of case ascertainment for oesophageal cancer was estimated with the mortality-incidence ratio (MIR). A ratio above unity is suggestive of under-registration of diagnoses. MIRs were determined for consecutive 5-year intervals from 1987 to 2011 for each cancer registry and provided no evidence for systematic under-registration [1]. MIRs ranged usually between 0.7 and 0.9 and were above or close to unity only for ZH and SG in time interval 1987-1996 and for BL/BS in time interval 1992-1996.

Observed survival (OS) and relative survival (RS) were derived for consecutive time intervals of increasing length after diagnosis during which the hazards were assumed to remain constant. Temporal divisions were 0.05, 0.1, 0.2, 0.4, 0.6, 1, 2, 3, 4, 5, and 6 years. RS was calculated as the ratio of the observed survival of cancer cases and the expected survival of persons in the general population matching in age, sex, calendar year of death and cantonal pool [3]. Expected cancer survival was estimated using the Ederer II method applied to all-cause mortality tables for the cantons combined [4]. All-cause death probabilities, transformed from age-, sex- and calendar year-specific death rates, were interpolated and smoothed using the

Elandt-Johnson formula [5]. RS ratios were estimated using the strs command (version 1.3.7) [6] written for the Stata Statistical Software [7]. Partially complete survival analysis was used for the comparison in Table 2. Since diagnoses from 2011 were excluded from this analysis, only 13 of 17 cantons were eligible. Period survival analysis [8] was used for the analysis of time trends in Table 3. Since it included diagnoses from 2011, all 17 cantons contributed to this analysis. In brief, partially complete analysis describes the survival of cases defined by dates of diagnosis, and period analysis defines cases by follow-up dates. RS estimates were age-standardized using weights specific for cancer of the oesophagus from the International Cancer Survival Standards (ICSS) [9]. Ninety-five percent confidence intervals (95% CI) were estimated using Greenwood's method [10] in partially complete analysis and in period analysis by applying the delta method to a transformation of the cumulative hazard. For age-standardized RS, 95% CI were estimated as described in [9].
To test for linear time trends of RS, the annual percentage change and its 95% CI was estimated with the Joinpoint Regression Program v4.0.4 [11].

Results

This report combines more than 8'500 person-years of survival experience for patients diagnosed with primary malignant cancer of the oesophagus (Tab. 1). The data pool contains increasing numbers of cancer registries over time. Until 1995, only the cantons AR, AI, BL, BS, GE, SG, and ZH contributed to the pool, whereas canton TI joined in 1996, canton FR in 2006, canton LU in 2010, and cantons OW, NW, UR and ZG in 2011. The cantons TI, VS, GR, GL, FR, LU, OW, NW, UR and ZG contributed less than 25% of the total cases.
Age at diagnosis ranged from 29 to 101 years. The median age at diagnosis was 66 years in men (interquartile range IQR 58-74) and 71 years in women (IQR 61-80). Neoplasms are more frequent at deeper anatomic subsites within the oesophagus, and overall, the most common primary malignancy was squamous cell carcinoma (61%), followed by adenocarcinoma (31%), other type (5%), and unspecified type (3%). Adenocarcinoma incidence increased in relative frequency from 29% to 39% if 1991-2000 is compared with 2001-2010, while squamous cell carcinoma incidence decreased from 62% to 53%, and proportions of other or unspecified histologic types remained constant. Information regarding tumour detection was available from the cantons GE, VS and FR and revealed that symptoms were responsible for detection in 88% of the cases.
The survival experience of men and women diagnosed with cancer of the oesophagus is shown in Tab. 2 for survival proportions at one and five years after diagnosis, and by survival curves in Fig. 1. The age-standardized relative survival (RS) proportions in men, diagnosed between 1991 and 2000, were 41.2% and 11.5% for one and five years after diagnosis, respectively. A decade later (2001-2010), the age-standardized RS had improved substantially to 51.1% and 18.5%, respectively. Age-standardized and age-specific relative survival (RS) proportions in women were slightly higher as compared with men, an advantage which declined with time of diagnosis. For diagnoses between 1991 and 2000, age-standardized RS in women were 44.2% and 17.9% for one and five years after diagnosis, respectively. A decade later (2001-2010), the improvement was somewhat less as compared with men, to 51.1% and 21.5%, respectively.
Temporal survival trends were analysed at higher resolution using five consecutive time periods of four year duration, starting in 1992 and ending in 2011 (Tab. 3). The annual percentage changes (APC) were significantly above

Table1: Number of malignant cases for cancer of the oesophagus used for survival analysis in the Swiss national dataset, stratified by Swiss cantons and age group. Seventeen cantons are covered by nine cancer registries.

Cantonal Cancer Registry	Available years of diagnosis	Number of cases							Person-years	% of pooled person-years
		00-59		60-74		75+		all ages		
		Men	Women	Men	Women	Men	Women	Both		
ZH/ZG	1980-2011	324	109	551	183	317	176	1660	2331	27.2
SG/AR/AI	1980-2011	176	21	280	46	151	52	726	1169	13.7
GE	1980-2011	234	52	276	91	145	99	897	1651	19.3
BS/BL	1981-2009	140	45	226	69	113	70	663	1292	15.1
TI	1996-2011	74	15	132	29	87	41	378	669	7.8
VS	1989-2011	111	17	163	41	86	42	460	822	9.6
GR/GL	1989-2011	63	7	112	24	70	27	303	424	5.0
FR	2006-2011	33	7	49	3	20	9	121	174	2.0
LU/UR/OW/NW	2010-2011	6	0	19	4	8	3	40	23	0.3
Total		1161	273	1808	490	997	519	5248	8555	100.0

Years since diagnosis	Age in years	Both			Men			Women		
		Relative survival %	95% CI [1] LL	UL	Relative survival %	95% CI [1] LL	UL	Relative survival %	95% CI [1] LL	UL
		Calendar period of diagnosis 1991 - 2000 [3]								
1	00-59	52.8	48.4	57.0	53.3	48.5	58.0	50.7	40.4	60.0
	60-74	44.4	40.5	48.2	43.6	39.1	47.9	47.8	39.5	55.7
	75 +	27.3	23.0	31.8	27.0	21.6	32.7	28.0	21.1	35.3
	all ages	42.6	40.2	45.1	43.5	40.6	46.3	40.6	35.8	45.4
5	00-59	19.0	15.2	23.1	18.0	13.9	22.7	23.0	14.4	32.8
	60-74	12.4	9.5	15.7	11.0	7.8	14.8	17.8	11.2	25.6
	75 +	4.7	2.3	8.4	1.9	0.3	6.8	7.6	3.4	14.1
	all ages	12.6	10.6	14.7	11.8	9.5	14.3	15.0	11.2	19.4
1	stand.[2]	42.0	39.5	44.4	41.2	38.3	44.0	44.2	38.9	49.3
5	stand.[2]	12.5	10.6	14.7	11.5	9.4	14.0	17.9	13.5	22.9
		Calendar period of diagnosis 2001 - 2010 [3]								
1	00-59	59.0	54.7	63.1	58.8	53.9	63.4	59.7	50.3	67.9
	60-74	54.7	51.6	57.7	55.3	51.8	58.7	53.1	46.3	59.4
	75 +	36.4	32.7	40.2	37.1	32.5	41.7	35.5	29.1	42.1
	all ages	50.3	48.2	52.4	51.3	48.8	53.7	47.7	43.4	51.8
5	00-59	25.5	21.5	29.8	23.0	18.5	27.8	34.2	25.3	43.3
	60-74	19.1	16.3	22.1	19.8	16.6	23.3	17.6	12.2	23.8
	75 +	10.2	7.4	13.5	9.7	6.3	14.1	11.3	6.8	17.1
	all ages	18.1	16.2	20.0	18.0	15.8	20.3	18.8	15.2	22.6
1	stand.[2]	50.92	48.7	53.1	51.1	48.5	53.7	51.1	46.6	55.3
5	stand.[2]	19.1	17.0	21.2	18.5	16.0	21.1	21.5	17.6	25.8

[1] CI (confidence interval); LL (lower limit); UL (upper limit)

[2] Age-standardized using ICSS weights

[3] Follow-up December 2001

[4] Follow-up December 2011

Table 2: Relative survival estimates after diagnosis of malignant cancer of the oesophagus, with 95% confidence intervals, by 10-year calendar period, age at diagnosis, years since diagnosis and sex. Data pooled from 13 Swiss cantons (AR, AI, BL, BS, FR, GE, GL, GR, LU, SG, TI, VS, and ZH).

zero for short term (one year after diagnosis) as well as for long term survival (five years after diagnosis). Persons above 60 years of age at diagnosis seemed to have gained less than younger patients if five-year RS is compared with one-year RS: the gap in RS at five year after diagnosis between age 75+ and <60 has widened from 8% to 22%, and between age 60-74 and <60 from -3 to 11%, while the one-year RS gaps by age remained the same.

Discussion

The main strength of our study is the large number of malignant primary oesophageal cancer cases that could be combined from seventeen Swiss cantons. The data spans 30 calendar years, thus allowing the analysis of changes over time. There are, however, important limitations to our study. We did not stratify survival by histological type of the primary tumour nor by progression stage of the disease due to limited data. In Switzerland we observed the same trend as in the Western world towards more adenocarcinoma compared to the squamous cell carcinoma. Because of slight survival advantages for cases of adenocarcinoma over squamous cell carcinoma [12], different case mix might have contributed to the observed positive trend in survival.

While age-standardized five year RS for men and women combined in Switzerland was close to the European mean for diagnoses during the Nineties of the 20th century, the RS moved to a position clearly above the European mean for diagnoses during the 1st decade of the 21st century. The 4th round of the European cancer registry-based study of cancer patients' survival and care, or EUROCARE-4 [13], estimated age-standardized five year RS for patients diag-

Years since diagnosis	Age in years	Relative survival [1] [%] Calendar period of death or censoring 1992-1995	1996-1999	2000-2003	2004-2007	2008-2011	APC [2]	[95% CI]
1	00-59	49.3	54.0	55.1	60.6	67.4	7.9	[4.9, 10.9]
	60-74	40.3	45.4	48.3	54.7	58.7	9.7	[7.8, 11.7]
	75+	23.5	26.1	31.3	33.4	40.2	14.4	[10.2, 18.7]
5	00-59	11.7	17.2	20.8	24.0	32.8	26.0	[17.5, 35.1]
	60-74	14.6	13.3	12.2	18.3	21.2	13.9	[-3.4, 34.2]
	75+	3.6	5.4	6.2	9.9	10.9	30.0	[14.9, 47.1]
1	stand.[3]	38.4	42.2	45.6	51.3	56.1	10.1	[8.9, 11.3]
5		11.2	12.5	13.0	19.0	22.1	20.6	[10.5, 31.7]

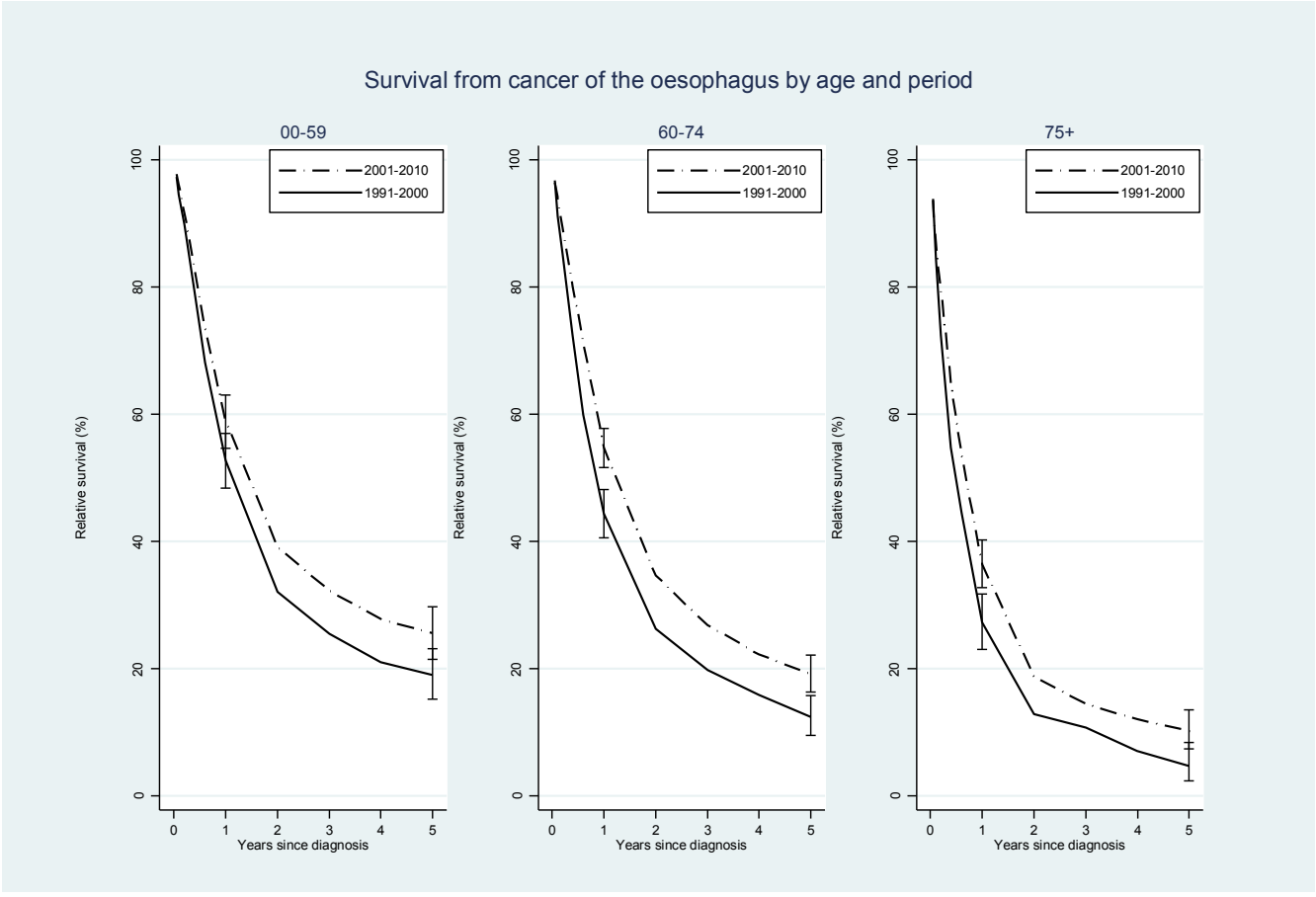
[1] Relative survival analysed with period approach.

[2] Annual percentage change. CI: confidence interval.

[3] Age standardized using ICSS weights

Table 3: Trends in relative survival for cancer of the oesophagus, expressed as the annual percentage change (APC). Cases for men and women were pooled from 17 Swiss cantons (AR, AI, BL, BS, FR, GE, GL, GR, LU, NW, OW, SG, TI, UR, VS, ZG, and ZH) for successive four-year calendar periods of follow-up.

Figure 1: Age-specific relative survival curves for two calendar periods of diagnosis (1991-2000 and 2001-2010). 95% confidence intervals are shown for survival proportions at one and five years after diagnosis. Cases of oesophageal cancer in men and women were pooled from 13 Swiss cantons (AR, AI, BL, BS, FR, GE, GL, GR, LU, SG, TI, VS, and ZH).



nosed with oesophageal cancer in 1995-1999 with 11.1%, which is close to the Swiss estimate of 12.5% for diagnoses in 1991-2000 (Tab. 2) or 1996-1999 (Tab. 3). While the updated EUROCARE-5 estimates of the European mean survival for patients diagnosed 2000-2007 remained low at 12.4% [14], estimates for Switzerland improved to 19.1% for patients diagnosed 2001-2010 (Tab. 2), or 19.0% for 2004-2007 (Tab. 3). There could be several reasons for this observation. Before 2001, patients in Switzerland were treated very heterogeneously. In 2002, the Swiss Group of Clinical Cancer Research (SAKK) started a series of clinical trials in the field of oesophageal carcinoma. Since then almost all clinical centers in Switzerland treating this type of cancer have participated in these SAKK activities. This has certainly led to better standardization of diagnosis and therapy in Switzerland and can explain some increase in quality of care. Other reasons for the increased survival over time are better patient selection and improved perioperative management. Most patients with newly diagnosed oesophageal carcinoma present with locally advanced disease. It remains a challenge to clinically stage these patients. For T-staging endosonography is regarded as the most accurate tool, whereas for N- and M-stage determination the combination of endosonography and PET-CT scan should be used. PET-CT scan detects about 10-20% distant metastasis not seen with conventional staging and is able to prevent this kind of surgery for some patients. In most European countries PET-CT is not registered for oesophageal cancer diagnostics. In Switzerland those diagnostic tools has been widespread and increased the accuracy of staging compared to some other European countries. Similar differences were seen in the peri- and postoperative management keeping in mind that oesophageal surgery is linked with a high perioperative risk for patients and full equipped, highly experienced intensive care unit is key.

In spite of some improvement in survival over time we have to recognize that survival with oesophageal carcinoma is still poor. The main reason is that most of the tumours already have systemic metastases at diagnosis. Progress over the last decade has been modest, and primarily reflects better patient selection and improved perioperative management. To accelerate progress, more research in this field is needed. In addition, public health interventions working towards changes in lifestyle factors associated with increased risk and worse survival, especially tobacco smoking [15, 16], might be beneficial.

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Krebsforscherin Nancy Hynes ab 2015 neue WiKo-Präsidentin

Kurt Bodenmüller, Krebsliga Schweiz

Ende 2014 endet die Amtszeit des Präsidenten der Wissenschaftlichen Kommision (WiKo), Prof. Dr. med. Martin F. Fey. Eine externe, unabhängige Evaluation hat der Arbeit des Fachgremiums, die während neun Jahren unter der Ägide des Direktors und Chefarztes der Universitätsklinik für Medizinische Onkologie am Berner Inselspital stand, kürzlich sehr gute Noten bescheinigt. In seine Fussstapfen tritt die renommierte Krebsforscherin Prof. Dr. Nancy Hynes, Forschungsgruppenleiterin am Friedrich Miescher Institut und Titularprofessorin für Molekularbiologie an der Universität Basel.

Im Juni bzw. Juli haben der Stiftungsrat der Krebsforschung Schweiz und der Vorstand der Krebsliga Schweiz Prof. Dr. Nancy Hynes einstimmig zur Präsidentin der Wissenschaftlichen Kommission (WiKo) gewählt. Das 17-köpfige Fachgremium evaluiert pro Jahr rund 170 Forschungs- und Stipendiengesuche aus allen Krebsforschungsbereichen nach klar definierten, wissenschaftlichen Kriterien. Basierend auf ihren Empfehlungen finanzieren die Vorstände von Krebsforschung und Krebsliga Schweiz jährlich gut 70 Projekte und Stipendiaten mit 14–15 Millionen Franken.

Überzeugende Nachfolgerin

Aus einer Liste mit 13 potenziellen Kandidatinnen und Kandidaten überzeugte Nancy Hynes die Vorstände in jeder Hinsicht. Von 1994 bis 2001 war sie bereits Mitglied der WiKo sowie 27 weiteren Gremien, Review Panels, Advisory und Editorial Boards, die sie zum Teil auch präsidierte. Ihr wissenschaftlicher Leistungsausweis ist tadellos: Hynes wies den höchsten h-Index von 67 aus, hat 183 Publikationen als Erst- bzw. Letztautorin veröffentlicht und die durchschnittliche Anzahl Zitierungen pro Publikation liegt bei 85 – ein Spitzenresultat. Die Biochemikerin ist eine weltweit anerkannte Expertin im Bereich der Signalübertragung bei Brustkrebs und im Speziellen des Her2-Rezeptors, der bei der Diagnose und Therapie des Mammakarzinoms eine wichtige Rolle spielt.

Prof. Dr. med. Martin F. Fey

Für ihre wissenschaftliche Leistung wurde Nancy Hynes mehrfach mit hochdotierten Forschungspreisen ausgezeichnet, darunter auch der Robert Wenner-Preis der Krebsliga Schweiz. Die US-Amerikanerin lebt seit ihrer Zeit als Post-Doc Ende der 70er-Jahre in der Schweiz. Obwohl sie selber keine Medizinerin ist, arbeitete sie aufgrund ihres Forschungsthemas lange und intensiv mit Klinikern zusammen. Die Förderung der translationalen Krebsforschung – die Verbindung von Laborforschung und Patientenbehandlung – war stets ein zentraler Schwerpunkt ihrer Arbeit. Nancy Hynes, die im Frühjahr 2015 pensioniert wird, ist somit eine Idealbesetzung für das Amt als WiKo-Präsidentin.

Eindrücklicher Leistungsausweis

Sie übernimmt den Stab von Martin F. Fey, der die WiKo von 2006 bis 2014 präsidiert hat. Sowohl seine Arbeit wie auch seine Art wurden von den Vorstands- und Kom-

Prof. Dr. Nancy Hynes

missionsmitgliedern rundum geschätzt. Kompromisslose «scientific excellence» war stets sein Massstab für die fachliche Begutachtung der Forschungsarbeiten. Engagiert hat sich der Onkologe aber nicht bloss für die Förderung der klinischen Forschung, sondern – neben der kompetitiven Grundlagenforschung – auch für epidemiologische und psychosoziale Forschungsarbeiten. Mit seinen klaren und mit spitzem Humor vorgetragenen Voten schaffte es Martin F. Fey, die WiKo-Mitglieder während den jeweils ganztätigen Sitzungen bei guter Laune zu halten.

Ende 2013 wurde eine umfangreiche Evaluation nach internationalen Standards der Forschungsförderung von Krebsforschung und Krebsliga Schweiz für den Zeitraum 1998-2012 veröffentlicht. Die international zusammengesetzte Expertengruppe würdigte in ihrem Bericht insbesondere die exzellente Arbeit der WiKo im Rahmen des Peer-Review-Verfahrens (siehe Artikel auf Seite 53-55 im Krebsbulletin vom März 2014). Gute Noten gab es auch seitens der Forschenden: Die überwiegende Mehrheit bezeichnete den Evaluationsprozess als transparent, fair und qualitativ gut. Die bibliometrische Analyse ergab ebenfalls erfreuliche Resultate: Ein Grossteil der unterstützten Projekte waren von ausgezeichneter Qualität und resultierten in vielen bedeutenden Publikationen – mit Topwerten im internationalen Vergleich. Für seine hervorragende Arbeit gebührt ihm seitens der Krebsforschung und der Krebsliga Schweiz ein herzliches Dankeschön.

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InfoMonat Brustkrebs: Neue Broschüre, neues Booklet, neue Aktion

Cordula Sanwald, Kommunikationsbeauftragte,
Krebsliga Schweiz

Der Oktober ist weltweit dem Thema Brustkrebs gewidmet. Die Krebsliga hat anlässlich des «Infomonats Brustkrebs» die neue, über 80 Seiten starke Broschüre «Brustkrebs - Mammakarzinom » herausgebracht. Begleitet wird sie von einem kleinen Booklet mit Übungen für Frauen nach einer Brustkrebsoperation.

In der Schweiz erhalten jedes Jahr rund 5500 Frauen die Diagnose Brustkrebs. Die neue Broschüre der Krebsliga «Brustkrebs – Mammakarzinom» möchte diesen Frauen und ihren Angehörigen eine erste Orientierung geben in einer Situation, in der das Leben ausser Balance gerät. Entsprechend umfassend ist die Publikation angelegt. Sie beschreibt eingangs grundlegend die weibliche Brust und ihre Funktion, geht auf gutartige Veränderungen und Knoten ein, um schliesslich die unterschiedlichen Formen von Brustkrebs darzulegen.

Die Frage nach der Ursache für und Anzeichen von Brustkrebs beschäftigt viele Frauen. Weil bislang jedoch keine eindeutigen Ursachen für Brustkrebs bekannt sind und es daher keine Methode gibt, um Brustkrebs zu verhindern, geht die Broschüre in diesem Zusammenhang vor allem auf jene Faktoren ein, die das Erkrankungsrisiko erhöhen und skizziert mögliche Beschwerden und Symptome.

Informationen und Hilfestellungen

Die Krebsliga hat grosse Erfahrung in der Beratung von Krebsbetroffenen und ihren Nächsten. Viel Raum nehmen in den Begleitungsgesprächen stets Erläuterungen ein, welche die Untersuchung, die Diagnose und den Therapieprozess bei Krebserkrankungen genauer erklären. Auch in der neuen Broschüre wurde diesen Fragen sorgfältig nachgegangen. So erhalten Lesende Informationen zu den ersten Abklärungen und den verschiedenen Untersuchungen, die zur genauen Diagnose führen. Erklärt werden auch die TNM-Klassifizierungen, die UICC-Krankheitsstadien sowie die weiteren Präzisierungen der Diagnosen.

Oft fällt es Betroffenen und ihren Nächsten schwer, in einer belastenden, akuten Phase die für sie wichtigen Fragen zu stellen. Die Broschüre gibt auch hier Hilfestellung, thematisiert den Umgang mit unerwünschten Wirkungen der Therapie und greift Themen auf wie Sexualität, Kinderwunsch oder Körperbild. Sie ermutigt zum Gespräch mit medizinischen wie psychoonkologischen Fachpersonen und unterstützt Betroffene bei der Vorbereitung auf solche Gespräche.

Behandlungsmöglichkeiten und Behandlungsablauf

Die Erkenntnisse der Forschung zu Brustkrebs in den letzten Jahren haben dazu geführt, dass Diagnosen immer präziser und die Therapien immer gezielter auf jede betroffene Frau abgestimmt werden. Die Vielzahl der heutigen Behandlungsmöglichkeiten stellen Betroffene allerdings oft vor Entscheidungsprobleme. Die Krebsliga-Broschüre zeigt die unterschiedlichen Behandlungsmöglichkeiten bei Brustkrebs auf und erklärt die Wirkungsweise der einzelnen Therapien. Sie skizziert, welche Therapie bei welcher Diagnose und in welchem Stadium in Frage kommt und stellt sachlich mögliche Folgen und Nebenwirkungen dar. Weitere Kapitel widmen sich einerseits den Behandlungsabläufen in verschiedenen Stadien, andererseits weiterführenden Behandlungen, welche zum Beispiel die Rekonstruktion der Brust oder eine Brustprothese ebenso im Fokus haben wie ein Lymphödem.

Ein ausführliches Verzeichnis mit Adressen von Beratungs- und Informationsstellen, mit Literatur-, Broschüren- und Internet-Hinweisen zu Brustkrebs bei Frauen und bei Männern runden die Publikation ab.

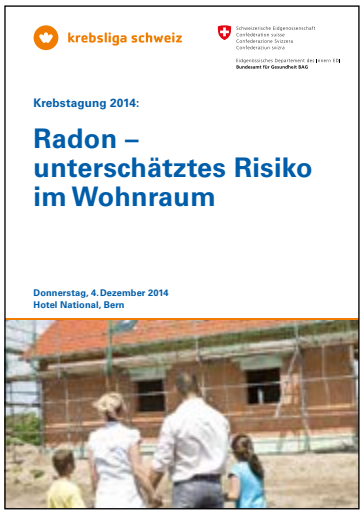
Bewegung tut gut

Bewegung spielt für krebsbetroffene Frauen eine wichtige Rolle. Es ist wissenschaftlich belegt, dass der Krankheitsverlauf bei Brustkrebsbetroffenen, die regelmässig körperlich aktiv sind, positiv beeinflusst werden kann. Darum liegt jeder Brustkrebs-Broschüre ein kleines Büchlein mit Übungen bei, die speziell nach einer Brustkrebsoperation sinnvoll sind. Das Büchlein «Bewegung tut gut» ist auch separat erhältlich.

Bestellung
«Brustkrebs- Mammakarzinom» sowie das Booklet «Bewegung tut gut» liegen derzeit erst in deutscher Sprache vor. Sie sind kostenlos erhältlich. Beides kann bei der Krebsliga bestellt werden. Sie erhalten die Publikationen auch bei den kantonalen und regionalen Krebsligen. www.krebsliga.ch Bestellungen unter Tel. 0844 85 00 00, shop@krebsliga.ch oder im Internet unter www.krebsliga.ch/broschueren

Radon – unterschätztes Risiko im Wohnraum

Patrizia Frei, Projektleiterin Umwelt und Tabak, Krebsliga Schweiz



Radon entsteht beim Zerfall von Uran im Erdreich. Dieses natürliche, radioaktive Edelgas, verursacht in der Schweiz jährlich 200 bis 300 Todesfälle durch Lungenkrebs. Mit baulichen Massnahmen bei Neu- und Umbauten kann die Radonbelastung in Innenräumen stark gesenkt werden. Die Krebstagung 2014 beleuchtet dieses wichtige Thema aus unterschiedlichen Blickwinkeln und gibt Fachpersonen aus Medizin, Public Health, Wissenschaft und aus dem Bauwesen die Möglichkeit, sich zu vernetzen.

Das natürliche, radioaktive Edelgas Radon gelangt vom Boden her in die Luft und ist unsichtbar, geruch- und geschmacklos. In der freien Umgebungsluft ist es unbedenklich für die Gesundheit. Es kann jedoch durch undichte Stellen in Bodenplatten und Kellerwänden in Häuser eindringen und sich dort anreichern.

Radonatome können weiter zerfallen. Werden diese radioaktiven Zerfallsprodukte eingeatmet, setzen sie sich in der Lunge fest und bestrahlen das Lungengewebe. Mit steigender Radonkonzentration erhöht sich das Risiko, an Lungenkrebs zu erkranken.

Lungenkrebs durch Radon

Die Ergebnisse von epidemiologischen Studien, die nach 1994 durchgeführt wurden, zeigen, dass das Risiko im Zusammenhang mit einer langfristigen Radonexposition in Wohnräumen grösser ist, als frühere Studien mit Bergarbeitern vermuten liessen. Aufgrund dieser Erkenntnisse empfahl die Weltgesundheitsorganisation 2009 eine maximale Konzentration von 300 Bq/m3, um das gesundheitliche Risiko infolge der Radonbelastung in Innenräumen zu verringern.

Den neuen Risikoeinschätzungen zufolge treten erhöhte Radonkonzentrationen in Innenräumen nicht nur in den bis anhin bekannten Risikogebieten der Alpen und der Jurakette, sondern in allen Regionen der Schweiz auf. Radon verursacht 8 bis 10 Prozent der Lungenkrebstodesfälle in der Schweiz, dies entspricht 200 bis 300 Todesfällen pro Jahr. Diese Anzahl ist vergleichbar mit der Anzahl an Todesfällen durch Melanome. Nach dem Rauchen ist Radon die häufigste Ursache für Lungenkrebs, für Nichtraucher stellt Radon gar den grössten Risikofaktor für Lungenkrebs dar.

Radonschutz in der Schweiz

Das Bundesamt für Gesundheit lancierte 2011 den nationalen Radonaktionsplan 2012–2020, mit dem Ziel, den Schutz der Schweizer Bevölkerung vor Radon sicherzustellen. Schlüsselelement des Aktionsplans ist die Revision der Strahlenschutzgesetzgebung, bei der die Grenzwerte angepasst werden sollen. Auch die Förderung des Radonschutzes im Bausektor stellt ein zentrales Element dar: durch geeignete Massnahmen bei Neu- und Umbauten lässt sich die Radonbelastung in Innenräumen mit wenig Aufwand erheblich senken.

Die Radonkonzentration kann sich beispielsweise auch als Folge einer energetischen Sanierung erhöhen, da das Edelgas durch die verbesserte Gebäudeabdichtung bzw. Isolation nur noch ungenügend aus dem Gebäude entweichen kann. Eine Abstimmung von Energie- und Radonsanierung ist somit unerlässlich. In Zukunft wird Radon auch in den Baunormen verankert werden.

Krebstagung 2014: Radon – unterschätztes Risiko im Wohnraum

Alle Bewohnerinnen und Bewohner der Schweiz können durch erhöhte Radonkonzentrationen belastet werden,

Radonschutz ist deswegen eine Notwendigkeit. Aus diesem Grund organisiert die Krebsliga Schweiz gemeinsam mit dem Bundesamt für Gesundheit und in Partnerschaft mit dem Schweizerischen Ingenieur- und Architektenverein (SIA) am ***4. Dezember 2014 im Hotel National in Bern*** eine Tagung zum Thema Radon.

Fachreferenten aus Medizin, Wissenschaft und Bauwesen beleuchten Radon und dessen Risiken aus unterschiedlichen Blickwinkeln. Die Tagung wendet sich an Fachleute und Interessierte aus Medizin, Public Health, Bauwesen und Wissenschaft sowie an Behördenvertreter, Hauseigentümer und Notare. Die Tagung wird mit einer Podiumsdiskussion abgeschlossen, an welcher u. a. Dr. Roland Charrière, Stv. Direktor des Bundesamtes für Gesundheit, und Prof. Dr. Jakob Passweg, Präsident der Krebsliga Schweiz teilnehmen.

Das Programm der Krebstagung 2014 sowie die Anmeldemodalitäten und weitere Informationen finden sich unter www.krebsliga.ch/krebstagung.

Krebstagung 2014: «Radon – unterschätztes Risiko im Wohnraum»

Donnerstag, 4. Dezember 2014, 9.15–16.30 Uhr
Hotel National in Bern

www.krebsliga.ch/krebstagung

Ein Anlass der Krebsliga Schweiz und des Bundesamtes für Gesundheit. Der Schweizerische Ingenieur- und Architektenverband (SIA) ist Partner der Tagung.

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Radon – un risque sous-estimé dans l'habitat

Patrizia Frei, responsable de projet Environnement et tabac, Ligue suisse contre le cancer

Le radon provient de la désintégration de l'uranium dans le sol. Ce gaz naturel radioactif provoque chaque année en Suisse 200 à 300 décès par cancer du poumon. Des techniques de construction permettent de réduire considérablement la concentration de radon dans les bâtiments neufs et rénovés. La Journée du cancer 2014 éclaire ce thème important sous différents angles et offre aux professionnels de la médecine, de la santé publique, de la science et du secteur du bâtiment la possibilité de se rencontrer.

Le gaz radioactif radon est naturellement présent dans le sol; ses émanations dans l'air sont invisibles, inodores et insipides. À l'air libre, il ne présente aucun risque pour la santé. Il peut cependant s'infiltrer par les défauts d'étanchéité de l'enveloppe des bâtiments et s'accumuler dans l'air ambiant. Lors de la respiration, les produits de désintégration du radon se déposent sur le tissu pulmonaire et l'irradient. Une concentration croissante de radon augmente ainsi le risque de contracter un cancer du poumon.

Cancer du poumon engendré par le radon

Les résultats de nouvelles études épidémiologiques réalisées dans l'habitat montrent que le risque, extrapolé à partir de données sur les travailleurs de mines, a jusqu'ici été sous-évalué. Sur la base de ces conclusions, l'Organisation mondiale de la santé a recommandé en 2009 une concentration maxi-

male de 300 Bq/m^3, afin de réduire les risques sanitaires liés au radon dans l'habitat.

Selon cette évaluation récente du risque, toutes les régions de Suisse sont désormais concernées par la problématique du radon, et plus seulement les régions à risque élevé des Alpes et de l'Arc jurassien définies jusqu'ici. Le radon génère 8 à 10 pourcent des décès par cancer du poumon, soit 200 à 300 cas par année en Suisse. Ce chiffre est comparable à celui des décès suite à des mélanomes. Le radon est la cause la plus fréquente de cancer du poumon après le tabagisme.

Protection contre le radon en Suisse

En 2011, l'Office fédéral de la santé publique a lancé le Plan d'action radon 2012–2020, dans le but d'assurer la protection de la population. L'élément-clé de ce plan d'action est la révision de la législation sur la radioprotection, dont les valeurs légales doivent être ajustées. Promouvoir la protection contre le radon dans le secteur du bâtiment est également un élément central: des techniques appropriées lors de la construction et des transformations permettent de réduire considérablement et facilement la concentration de radon dans les bâtiments.

Cette concentration peut également augmenter, par exemple suite à un assainissement énergétique, étant donné que la ventilation naturelle du bâtiment sera entravée. Un compromis entre l'assainissement énergétique et le radon est donc indispensable. À l'avenir, le radon sera également intégré dans les normes de construction.

Journée du cancer 2014: Radon – Un risque sous-estimé dans l'habitat

Toute la population suisse peut être exposée à des concentrations accrues de radon. La protection contre ce gaz est par conséquent nécessaire. Dans ce cadre, la Ligue suisse contre le cancer organisera une journée sur le thème du radon le ***4 décembre 2014 à l'Hôtel National de Berne***, en collaboration avec l'Office fédéral de la santé publique et en partenariat avec la Société suisse des ingénieurs et des architectes (SIA).

Des intervenants spécialisés dans les domaines de la médecine, de la science et du bâtiment apporteront chacun leur éclairage sur les risques liés au radon. Cette journée s'adresse aux professionnels de la médecine, de la santé publique et de la construction, aux scientifiques, aux personnes intéressées, ainsi qu'aux représentants des autorités, aux propriétaires immobiliers et aux notaires. Elle se terminera par un débat public auquel participeront, entre autres, le Dr Roland Charrière, directeur suppléant de l'Office fédéral de la santé publique et le Prof. Jakob Passweg, président de la Ligue suisse contre le cancer.

Vous trouverez le programme de la Journée du cancer 2014, les modalités d'inscription et des informations complémentaires sous www.liguecancer.ch/journeeducancer.

Journée du cancer 2014: «Radon – Un risque sous-estimé dans l'habitat»

Jeudi 4 décembre 2014, 09.15-16.30 h
Hôtel National, Berne

www.liguecancer.ch/journeeducancer

Un événement de la Ligue suisse contre le cancer et de l'Office fédéral de la santé publique, en partenariat avec la Société suisse des ingénieurs et des architectes (SIA).

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Im Oktober sieht die Schweiz Pink!

Im Oktober 2014 mobilisiert die Krebsliga die ganze Schweiz zur Solidarität mit Brustkrebsbetroffenen. Mit der Aktion «Die Schweiz sieht Pink – bekenne Farbe» baut die Krebsliga eine neue Community-Plattform auf, um den von Brustkrebs betroffenen Frauen und ihren Angehörigen und Freunden einen Raum des Austauschs zu bieten. Gleichzeitig ermöglicht diese Plattform allen Interessierten, ihre Solidarität durch eigene Aktionen oder durch die Teilnahme an Veranstaltungen konkret kundzutun.

Eine neue pink-farbige Community-Plattform,

… um Emotionen zu teilen!

Unter dem Motto «Die Schweiz sieht Pink – bekenne Farbe» lädt die Krebsliga Brustkrebsbetroffene, ihre Angehörigen und alle Interessierten ein, ihre Hoffnungen, ihre Wünsche und ihre Trauer auf der neuen Community-Plattform zu teilen: www.krebsliga.ch/brustkrebs (ab 1. Oktober 2014).

… um private-Solidaritätsaktionen anzukünden!

Im Oktober sind alle Interessierten aufgerufen, eine persönliche Aktion zur Solidarität mit Brustkrebsbetroffenen durchzuführen und diese auf der Community-Plattform bekanntzumachen: Pink-farbige Muffins backen und verkaufen, Haare pink färben, die persönliche Facebook-Seite pink einfärben, ein Konzert zugunsten der Krebsliga geben – dem Einfallsreichtum sind keine Grenzen gesetzt.

… um sich solidarisch zu zeigen!

Weiter kann die Bevölkerung an verschiedenen Aktionen oder Aktivitäten teilnehmen, die von der Krebsliga und ihren kantonalen und regionalen Ligen, von Partnern oder von Privatpersonen auf der Plattform angeboten werden. Die Aktionen finden alle im Oktober statt. Ihren Höhepunkt erreichen sie am 23. Oktober, an dem sich die Schweiz aufgrund der zahlreichen Aktionen ganz in pink präsentieren wird.

Alle diese Aktionen werden auf der Community-Plattform beworben und dokumentiert.

www.krebsliga.ch/brustkrebs

Im Oktober sieht die Schweiz Pink.

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En octobre, la Suisse voit rose!

En octobre, la Ligue contre le cancer invite toute la Suisse à se mobiliser pour témoigner sa solidarité aux personnes touchées par le cancer du sein. A travers l'action «La Suisse voit rose», elle met en place une nouvelle plateforme communautaire qui poursuit un double objectif: offrir aux femmes concernées et à leurs proches et amis un espace de partage, mais aussi permettre à tous les intéressés de faire connaître leur soutien en organisant des actions ou en participant à des activités.

Une nouvelle plateforme communautaire en rose pour…

… partager ses émotions

Sous le slogan «La Suisse voit rose», la Ligue contre le cancer invite les femmes touchées par le cancer du sein, leurs proches et tous les intéressés à partager leurs espoirs, leurs souhaits et leur tristesse sur la nouvelle plateforme communautaire: www.liguecancer.ch/cancerdusein (dès le 1er octobre).

… annoncer des actions personnelles de solidarité

En octobre, toutes les personnes intéressées sont invitées à mettre sur pied une action personnelle en signe de solidarité avec les femmes touchées par le cancer du sein et à le faire savoir sur la plateforme communautaire: confectionner et vendre des muffins roses, se teindre les cheveux en rose, afficher sa page facebook en rose, donner un concert au profit de la Ligue contre le cancer… il n'y a pas de limite à l'expression de la solidarité!

… participer au mouvement de solidarité

La population pourra par ailleurs participer à différentes actions ou activités organisées par la Ligue suisse et les ligues cantonales et régionales contre le cancer, par des partenaires ou des particuliers. Toutes les actions se dérouleront en octobre et trouveront leur point culminant le jeudi 23: ce jour-là, grâce aux nombreuses actions mises en place, toute la Suisse se présentera en rose.

Toutes ces actions seront annoncées et documentées sur la plateforme communautaire.

www.liguecancer.ch/cancerdusein

En octobre, la Suisse voit rose!

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Fort- und Weiterbildungen der Krebsliga Schweiz
Formation continue de la Ligue suisse contre le cancer

«INTERPROFESSIONELLE WEITERBILDUNG IN PSYCHOONKOLOGIE»

In folgenden Einzel-Workshops hat es freie Plätze:

23.10.2014 Inselspital, Wirtschaftsgebäude, Bern
Ganzer Tag: Einführung in die Psychoonkologie: Konzepte und Onkogenese

20.11.2014 Haus der Krebsliga, Bern
Nachmittag: Brustkrebs / Hoden CA / Melanom

11.12.2014 Haus der Krebsliga, Bern
Nachmittag: Allgemeine Tumoreinteilung und Staging, Lungenkrebs, HNO-Krebs

19.03.2015 Inselspital, Wirtschaftsgebäude, Bern
Vormittag: Onkologische Behandlung (Prostata CA / Lymphome, Nieren CA)
Nachmittag: Männerbetreuung

23.04.2015 Haus der Krebsliga, Bern
Nachmittag: Genetische Prädisposition: Wie beraten?

21.05.2015 Inselspital, Wirtschaftsgebäude, Bern
Vormittag: Hämatologie / Nachmittag: Folgen der Isolation

18.06.2015 Inselspital, Wirtschaftsgebäude, Bern
Vormittag: Coping, Lebensqualität (kognitive Störungen, Umgang mit Persönlichkeitsveränderungen)
Nachmittag: Hirntumoren

Information und Anmeldung für Lehrgang und Einzel-Workshops: Loredana Palandrani, Krebsliga Schweiz, Kursadministration, Tel. 031 389 93 27, kurse-cst@krebsliga.ch

«KOMMUNIKATIONSTRAINING»

Seminar für Ärztinnen, Ärzte und Pflegefachleute von Krebskranken

Teilnehmende sind onkologisch erfahrene Fachkräfte, die ihre Kommunikationstechniken verbessern möchten.

Nr. 146 30.–31.10.2014 Sorell Hotel Aarauerhof, Aarau

Das Seminar wird von der SGMO für den FMH-Titel Onkologie gemäss Weiterbildungsstatut akzeptiert. Diverse medizinische Fachgesellschaften vergeben Fortbildungspunkte/Credits.

Information und Anmeldung: Loredana Palandrani, Krebsliga Schweiz, Kursadministration
Tel. 031 389 93 27, kurse-cst@krebsliga.ch

Kommunikation mit krebskranken Jugendlichen und deren Eltern

Trainingsseminar für pädiatrische Onkologen und Onkologiepflegende

21.-22.11.2014 Hotel Bildungszentrum 21, Basel

Angefragt wurde die Schweizerische Gesellschaft für Pädiatrie, die das Seminar bisher mit 12.5 Credits als fachspezifische Kernfortbildung anerkannt hat.

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No 229 27.–28.11.2014 Hôtel Préalpina, Chexbres

Ce séminaire est reconnu par la SSOM pour le titre FMH en oncologie, en accord avec les statuts régissant la formation continue. Différentes sociétés médicales reconnaissent ce séminaire et lui octroient des crédits de formation continue.

Information et inscription: Loredana Palandrani, Krebsliga Schweiz, Kursadministration
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Tagungsbericht zur 11. Schweizer Fachtagung Psychoonkologie vom 10. April 2014 in Olten

Theresa Tondorf, Unispital Basel, Onkologie

Mitglieder des Organisationsteams und Helferinnen

Das Thema der diesjährigen Fachtagung «Der Angst den Schrecken nehmen» stiess auf reges Interesse. Die Tagung war lange vor Anmeldeschluss ausgebucht und mit 150 Teilnehmern sehr gut besucht. Der Tag begann mit der Mitgliederversammlung der SGPO, bei der die drei langjährigen Vorstandsmitglieder Urs Stillhard, Christine Beer und Regula Ursprung mit einem grossen Dankeschön für ihr grosses Engagement und ihre Arbeit verabschiedet wurden. Dem Vorschlag des Vorstandes, Ruedi Schweizer und Lucia Stäubli neu in den Vorstand aufzunehmen, stimmten die anwesenden Mitglieder ohne Gegenstimme zu.

Als erstes referierte Judith Alder, die Präsidentin der SGPO und psychologische Psychotherapeutin in eigener Praxis, zum Thema «Krebskrank – Angstkrank?». Sie betonte darin, dass Angst eine der wichtigsten Emotionen unserer Existenz sei und sich vielfältig ausdrücke. Bei einer Krebserkrankung würden Ängste genährt durch eine existentielle Komponente: die Möglichkeit, dass diese Krankheit das Ende des eigenen Lebens bedeuten könnte. Es sei für Betroffene und Angehörige, aber auch für Behandelnde wichtig, die biologischen Grundlagen dieser existentiellen Angst zu verstehen. Frau Alder präsentierte einige der wichtigsten und neusten Erkenntnisse zu den biologischen Grundlagen der Angst und ermöglichte den Teilnehmenden, ihr Wissen zu erweitern.

Im zweiten Referat des Morgens wies Bärbel Gründobler, Ärztin für Psychosomatische Medizin und Psychotherapie an der Technischen Universität München, auf eine besondere Form der Angst hin, der Angst vor dem Fortschreiten oder der Rückkehr der Erkrankung, auch Progredienzangst genannt. Frau Gründobler gewährte in ihrem Vortrag sowohl einen Einblick in die aktuelle Forschung der Progredienzangst als auch in die Behandlung dieser spezifischen Angst in Form eines gruppentherapeutischen Angebotes.

Am Nachmittag folgte ein vielfältiges Angebot an Parallelworkshops, die eine vertiefte Auseinandersetzung boten. Folgend die Auswahl an Themen: Hilf mir zu verstehen – systemisch-psychotherapeutisches Verständnis der Angst in einem komplexen Behandlungssystem; Freiräume in der Angst schaffen durch Meditation; musiktherapeutische und psychologische Interventionen in der pädiatrischen Onkologie; Progredienzangst bei onkologischen Erkrankungen – ein gruppen-therapeutischer Ansatz; Angst am Lebensende: Die Angst vor dem Tod, dem Nicht mehr Sein und die vielfältigen Aspekte der Furcht im Sterbeprozess.

Inspiriert und ausgestattet mit Ideen zu Behandlungsansätzen, fanden sich die Teilnehmenden nach den Workshops zum Abschlussvortrag von Frau Christa Diegelmann, psychologische Psychotherapeutin in eigener Praxis und Fortbildungsleiterin am Institut für Innovative Gesundheitskonzepte in Kassel. Sie berichtete «Vom kreativen Umgang mit der Angst in der Psychoonkologie». Sie hob darin die Relevanz von Ressourcen und der Kreativität bei der Behandlung von Krebserkrankungen hervor. Die Aktivierung von Ressourcen könne als eine Form der «Entängstigung» wirken und Kreativität fördern. Reduzierter Stress, sowie höhere kognitive und emotionale Flexibilität sei die Folge und eine damit einhergehend gestärkte Resilienz.

Das Organisationskomitee dieser Fachtagung kann auf einen durch und durch gelungenen Tag zurückblicken mit einem vielfältigen Programm und der Möglichkeit eines regen Austauschs unter Fachpersonen. Die nächste Fachtagung der SGPO wird am 16. April 2015 stattfinden und sich mit dem Thema «Würde» im Umgang mit und in der Behandlung von Krebserkrankungen auseinandersetzen.

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Zertifizierungsprozess «Swiss Cancer Network» ist gestartet

Walter Mingrone, Kantonsspital Olten
Vorstandsmitglied Swiss Cancer Network

Die moderne Behandlung von Krebskrankheiten ist durch eine zunehmende Spezialisierung geprägt. Aber kennt jeder Leistungserbringer die Möglichkeiten des anderen Spezialisten wirklich? Wohl kaum, weshalb die meisten Kolleginnen und Kollegen interdisziplinäre Fallbesprechungen wie Tumorboards nicht in Frage stellen[1]. An Tumorboards bringen die verschiedenen Spezialisten breit gefächertes Wissen und Erfahrung in die Diskussion ein. Die gemeinsame Besprechung ermöglicht zudem eine individuell abgestimmte Koordination zur Abklärung und Behandlung des Patienten. Während der Nutzen des Tumorboards auf das Outcome des Patienten schwierig zu belegen ist, führt die Befolgung von Guidelines nachgewiesenermassen zu besseren Behandlungsergebnissen[2,3,4].

Im Schweizerischen Umfeld sind die Medizinischen Onkologen in der freien Praxis wie auch in allen Spitälern sehr häufig diejenige Spezialisten, welche die Rolle des «Disease Managers» für den Patienten übernehmen. Es erstaunt deshalb wenig, dass gerade aus dem Umfeld der Medizinischen Onkologie die Initiative zur Gründung des Swiss Cancer Network entstanden ist.

Swiss Cancer Network

Das Swiss Cancer Network (SCN) ist 2012 aus einer Initiative der Schweizerischen Gesellschaft für Medizinische Onkologie (SGMO) entstanden und hat sich verschiedene Ziele für die Förderung des interdisziplinären Austauschs, der Zusammenarbeit sowie der Qualitätskontrolle gesetzt. So will das SCN unter anderem dazu beitragen, ausgewählte Ziele des Nationalen Krebsprogramms 2014-2017 zu erreichen. Das SCN bezweckt, dass eine Evidenz- und Guideline-basierte Behandlung über die ganze Behandlungskette koordiniert und gewährleistet wird und die Behandlungsqualität gefördert wird, bei gleichzeitig wohnortsnaher Versorgung des Patienten[5].

Mit dem Quality Oncology Practice Initiative Certification Program der ASCO wird in den USA bereits seit einigen Jahren ein sehr ähnliches Projekt erfolgreich vorangetrieben[6].

Zertifikat Swiss Cancer Network

Das Zertifikat Swiss Cancer Network bezweckt, die Behandlungs- und Betreuungsqualität für Tumorpatienten zu fördern. Interdisziplinäre, Prozess-orientierte Entscheidungsfindung sowie Respektierung anerkannter Guidelines sind die Basis der Qualitätskriterien. Diese fanden bei der Urabstimmung der SGMO am 15. Januar 2014 eine 87%-ige Zustimmung (40% Stimmbeteiligung).

Das Zertifikat wird an Einrichtungen vergeben, die Krebspatienten behandeln und diagnostische und therapeutische Entscheide in einem Tumorboard erarbeiten.

Mitglieder, die das Zertifikat erwerben, dokumentieren unter anderem

- dass sie ihre Tumorpatienten gemäss international anerkannten Richtlinien behandeln und betreuen,
- ihre Patienten in interdisziplinären Tumorboards besprechen,
- eine strukturierte Zusammenarbeit mit Querschnittsfächern betreiben,
- ihre Bereitschaft, ihre Behandlungsdaten im Rahmen eines Qualitätsregisters offenzulegen.

Das SCN ist für die Umsetzung des Zertifikats zuständig. Die zertifizierten Institutionen müssen sich einem Audit unterziehen, das von einer unabhängigen Auditstelle (SanaCERT Suisse) unter Beizug von Peers (Onkologen mit mindestens 5 Jahren Berufserfahrung) stichprobenweise geführt wird.

Ab dem 1. Juli 2014 kann das Zertifikat beantragt werden. Die initiale Vergabe erfolgt aufgrund einer Selbstdeklaration, die in jährlichem Abstand erneuert werden muss.

Ausblick

Nach vielen internen Diskussionen, Gesprächen mit Fachleuten von Akkreditierungs- und Zertifizierungsstellen, dem Studium von ausländischen Modellen und organspezifischen Zertifizierungen sind wir überzeugt, mit dem Zertifikat ein Instrument geschaffen zu haben, welches die Schlüsselelemente einer hochstehenden onkologischen Versorgung widerspiegelt.

So wie die SAKK ein Netzwerk für die klinische Forschung ist, so soll das SCN eine Plattform für die hochstehende onkologische Versorgung *aller* Tumorpatienten sein. Unsere Ziele können nur durch gegenseitigen Respekt und unter Einbezug aller Disziplinen erreicht werden. Dafür setzt sich das SCN ein. Alle, die an Krebs erkrankte Menschen behandeln und betreuen, sind herzlich eingeladen, dieses Netzwerk zu nutzen und weiter zu entwickeln.

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IBCSG SOFT and TEXT: aromatase inhibitor question presented at ASCO

Rudolf Maibach, IBCSG Coordinating Center, Berne

Keywords: metastatic breast cancer, chemotherapy, endocrine treatment, quality of life, pregnancy

The TEXT and SOFT trials are phase III, randomized clinical trials that enrolled 2,672 and 3,066 premenopausal women with hormone receptor-positive early breast cancer, respectively, between November 2003 and April 2011. Over 500 medical institutions from 27 countries enrolled women in the trials. Fourteen SAKK centers and private practices included 114 patients in SOFT and 165 patient in TEXT. In the two trials, 4,690 women were randomized to 5 years adjuvant treatment with exemestane+ovarian function suppression or with tamoxifen+ovarian function suppression.

Treatment with an aromatase inhibitor has previously been demonstrated to be beneficial to postmenopausal breast cancer patients compared with tamoxifen. TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function Trial) were conducted to determine whether this benefit could be extended to premenopausal women by combining exemestane with ovarian function suppression.

After a huge effort to update the clinical documentation of the patients, the two trials were finally ready for analysis earlier this year. They were designed to be complementary and were conducted over the same time period, in the same general population, and have these two treatments in common. IBCSG decided to merge the data of the two trials which address the aromatase inhibitor question in order to analyze the data earlier than would have been possible by separate analyses, and submitted a late-breaking abstract to ASCO.

On Sunday June 1, Olivia Pagani from Istituto Oncologico della Svizzera Italiana presented the results in the plenary session. Treatment with exemestane plus ovarian function suppression reduced the risk of developing any invasive cancer by 28%, and reduced the risk of developing invasive breast cancer recurrence by 34%, compared to treatment with tamoxifen plus ovarian function suppression. At 5 years from study entry, 92.8% of women remained free from breast cancer after treatment with exemestane plus ovarian function suppression; 88.8% after tamoxifen plus ovarian function suppression. Olivia concluded that exemestane+OFS, as compared with tamoxifen+OFS, significantly improves disease-free survival, breast cancer free interval and distant relapse free interval and is therefore a new treatment option for premenopausal women with hormone-receptor positive early breast cancer. The publication of the results was e-published on the same day by New England Journal of Medicine.

Olivia Pagani, IOSI

Both trials also included a Quality of Life part. Jürg Bernhard and colleagues presented first results of the substudy in a poster. Patients on tamoxifen+OFS were significantly more affected by hot flushes than exemestane+OFS, a difference which persisted over time. Throughout treatment, patients on exemestane+OFS reported more vaginal dryness and greater loss of sexual interest, while tamoxifen+OFS resulted in more vaginal discharge. The difference between treatments in bone/joint pain was most pronounced in the short-term in favor of T+OFS, but a difference persisted over time. Changes of global QoL indicators (mood, physical wellbeing, and coping effort) from baseline were similar between treatments over the whole treatment period. Jürg concluded that there is no strong indication to favor either treatment option from a quality of life perspective, and that the efficacy benefit of the aromatase treatment is achieved without an overall impact on quality of life. The differential effects of the two treatments on endocrine symptoms burden need to be addressed with patients individually.

The SOFT-EST substudy was conducted to describe estradiol (E2), estrone (E1) and estrone sulphate (E1S) levels during the first 4 years of trial treatments triptorelin+exemestane and triptorelin+tamoxifen, and to possibly identify a group of patients on trip+exe with suboptimal estrogen suppression. The substudy was conducted in collaboration with the SOLTI group (Spain) and Meritxell Bellet from Hospital Vall d'Hebron, Barcelona, presented in a poster the results of the first 12 months of observation. Under triptorelin+exemestane, the median reductions from baseline in E2, E1 & E1S levels were >95% at 3, 6 and 12 months after start of treatment, and significantly lower than in triptorelin+tamoxifen. A group of 27 out of 79 trip+exe patients with ≥1 post-

baseline sample had E2 levels >2.72 pg/mL at least once, and 2 had vaginal bleeding for longer than 3 months beyond start of treatment, 1 with suboptimal estrogen suppression (SES). Baseline factors related to SES in trip+exe were no prior chemo, high BMI, low FSH & LH, but not age. The conclusion was that most pts on trip+exe reached an E2 level below the defined threshold, consistent with postmenopausal pts on an AI, but some may be suboptimally suppressed. The clinical relevance of this finding will be further explored with the full 4 years of estrogen results and outcome data.

CLINICAL TRIALS

IBCSG 38-09/ BIG 3-07/ TROG DCIS

This randomized phase III study of radiation doses and fractionation schedules for ductal carcinoma in situ (DCIS) of the breast is conducted by IBCSG in Switzerland and Italy on behalf of the Trans Tasman Radiation Oncology Group TROG. Women with completely excised non-low risk ductal carcinoma in situ (DCIS) treated by breast conserving surgery suitable for adjuvant whole breast radiation therapy (RT) are eligible for the study. The trial explores the value of adding a tumor bed boost to whole breast RT, and compares a shorter vs a standard dose fractionation schedule in a two by two design.

The recruitment rate was well above expectations and in July 2014 the recruitment was closed after 1608 patients. Eight Swiss radio-oncology units have recruited a total of 55 patients. Treatment of the last patients continues and every patient will be followed up for 10 years after randomisation. One interim analysis of the trial endpoints is planned to take place after 50% of the expected local recurrences have occurred, estimated to occur at approximately one year after the end of accrual. The main analysis of endpoints time to local recurrence, time to disease recurrence, cosmetic outcome, toxicity, quality of life, but not yet overall survival will take place in 2019. Patients will then be followed yearly for a further 5 years, at the end of which the analysis of overall survival will take place together with an updated analysis of the other study endpoints.

IBCSG 42-12 SNAP

The trial evaluates in a randomized phase II fashion three different schedules of nab-Paclitaxel in patients with histologically or cytologically confirmed HER2-negative metastatic (stage IV) breast cancer who have not received any prior chemotherapy. The acrynom stands for Schedules of NAb-Paclitaxel. It is planned to recruit 240 patients within about 30 months.

SNAP evaluates three schedules of nab-Paclitaxel as prolonged chemotherapy administration strategy. All three arms start with a common induction treatment during the first 3 cycles, and then continue with different schedules of reduced dose intensity until progressive disease or lack of tolerability. Each of the three arms will be compared to a historical reference of seven-month median PFS based on the most recent trial with docetaxel as control arm to determine whether any of the three arms are worthy of further investigation.

The trial is being conducted in several European countries. The first patient was randomized in April 2013, and by June 30, 2014, 121 patients have been recruited. Nine SAKK sites participate, and recruited 29 patients until June.

Based on recommendations from the IBCSG Data and Safety Monitoring Committee (DSMC), IBCSG has decided to adapt the dose of nab-Paclitaxel in the induction phase, and asks to carefully consider comorbidities when screening new patients. The corresponding amendment has been issued and will be activated in the next few months.

IBCSG 43-09 HOHO

IBCSG 43-09 is the Young Women's Breast Cancer Study, and HOHO stands for «Helping Ourselves Helping Others». It is a longitudinal cohort study of 300 young women with breast cancer (early or advanced) in selected institutions in Europe. All eligible patients treated at each center are invited to join the cohort. Patient surveys and medical record review are utilized. Women are surveyed every 6 months for the first 3 years after diagnosis, then yearly thereafter for an additional 7 years (for a total follow-up of 10 years following diagnosis). The study has two main objectives:

1. To identify in selected institutions in Europe a cohort of young women (age 18-40) newly diagnosed with breast cancer (early or advanced) to assess a broad range of variables at baseline and over the course of the ensuing 10 years.

2. To characterize this population at diagnosis and in follow-up regarding disease and psychosocial outcomes (e.g., presentation and disease characteristics, fertility and menopausal issues, and long term outcome).

At present 11 centers in Italy and 4 centers in Switzerland are participating in the trial and have accrued 213 patients up to end of June 2014, 54 of them by Swiss sites.

IBCSG 48-14/BIG 8-13 POSITIVE

The best available evidence suggests that pregnancy after breast cancer does not negatively impact disease outcome and is safe for the offspring but no definitive information is available to recommend a safe interval from BC diagnosis to pregnancy. The POSITIVE trial will investigate endocrine therapy (ET) interruption to enable conception for young women between 18 and 42 years of age with endocrine responsive early breast cancer who received adjuvant ET for 18 to 30 months and wish to attempt pregnancy. The main objectives are:

- To assess the risk of breast cancer relapse associated with temporary interruption of endocrine therapy to permit pregnancy
- To evaluate factors associated with pregnancy success after interruption of endocrine therapy.

The trial will also allow for the testing of biologic correlates of pregnancy and disease outcome.

A psycho-oncological companion study evaluating psychological distress, fertility concerns and decisional conflict in young women who participate in POSITIVE has been developed and will be activated in sites interested and capable to conduct it. The participation of the US-American Alliance Group is anticipated and will be negotiated in the months to come.

A total of 500 patients are planned to be recruited into the trial from centers worldwide in approximately 4 years. The trial activation package has been sent to more than 60 interested sites and all IBCSG centers on July 3.

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ETOP: Five years of successful growth

Solange Peters, ETOP Communication Chair and Scientific Coordinator

Keywords: Non small cell lung cancer, small cell lung cancer, translational research, chemotherapy, radiotherapy

The interest in promoting and improving collaboration in clinical and translational research in lung cancer and mesothelioma in Europe prompted investigators representing collaborative study groups and institutions concerned with thoracic malignancies to explore new ways of working together. Out of this discussion the European Thoracic Oncology Platform was founded in 2009. This was the final step after two years of consultation between friends and leaders in the field of thoracic oncology throughout Europe. While Rolf Stahel as President of the Foundation Council and chair of the Scientific Committee and Solange Peters as Scientific Coordinator are the driving forces behind this effort, it is important to note that without the contribution of a large number of investigators, the Statistical Office lead by Urania Dafni and the staff at the Coordinating Office in Bern it would have not have been possible to get where we are.

Since 2009 ETOP has continuously enlarged its membership and now comprises more than 50 collaborative groups and institutions from all over Europe, as well as two large and eminent institutions outside Europe, one in the United States (Roswell Park) and one in China (Shanghai Chest Hospital).

In these pioneer years ETOP has evolved greatly in several ways. The first major undertaking which was started is Lungscape, a project to study the molecular epidemiology of lung cancer in Europe. Seventeen major cancer centers have created a decentralised biobank of tumor samples from over 2700 patients who are fully documented with comprehensive demographic and clinical data. A succession of so-called Lungscape Modules is being implemented to study a variety of biomolecular markers with the ultimate goal of identifying targets for latest-generation substances. The innovative approach of combining local sample collections into one virtual biobank with a centralised database of clinical parameters collected uniformly by all participants has generated a lot of enthusiasm not only among oncologists but also their colleagues in the pathology departments by providing them with an excellent opportunity to take part in highly competitive translational research.

From the start, ETOP also strived to present a platform for the exchange of knowledge and for dissipation of latest insight on thoracic malignancies. First of all, www.etop-eu.org is the place where ETOP members find a valuable collection of scientific evidence. Slide sets summarising the most important presentations from major cancer conferences like ASCO, ESMO, WLCC and ELCC are compiled by a series of editors within a few days of these events. Moreover, the editors select the most important publications and present them briefly on the ETOP website. In addition, ETOP members have free access to the Lung Cancer Journal.

The ETOP Residential Workshop brings together young investigators and experienced faculty and allows in an informal setting to develop and discuss with peers new ideas for clinical research. This format is a great opportunity for the next generation of researchers to improve their skills and to network.

Early on ETOP has also decided to advance clinical research by conducting therapeutic trials in collaboration with its members. Several approaches have been taken which all have their merits. ETOP conducts its own trials and sponsors them; examples are EMPHASIS and STIMULI, the latter being performed in collaboration with IFCT (Intergroupe Francophone de Cancérologie Thoracique) as the potential largest contributor. The BELIEF trial is sponsored by ETOP, but coordinated by the Spanish Lung Cancer Group (SLCG). EORTC is in charge of the conduct and evaluation of the SPLENDOUR trial, whereas ETOP still sponsors this trial. Each trial is financially supported by a pharmaceutical company, and ETOP and its partners vouch for the academic independency in the conduct, evaluation and publication of the results. The safety of the patients participating in these trials is assessed semi-annually by ETOP's Independent Data Monitoring Committee.

The members of ETOP are either single academic hospitals and clinics or collaborative groups like EORTC, SAKK, SLCG, IFCT, the All Ireland Co-operative On-

cology Research Group ICORG or the Central European Collaborative Oncology Group CECOG. Such groups take over some of the responsibilities in the projects and often act as intermediary between ETOP and their own sites. This provides the necessary flexibility to take into account local requirements and traditions and allows conducting research in a way which is familiar for the respective investigators and their staff.

In order to complete the various tasks entailed by all these projects, ETOP has undergone a strategic collaboration with IBCSG and its Coordinating Center in Bern. The ETOP Coordinating Office is able to support all activities in the above projects. In addition, Frontier Science Hellas, a non-profit organisation based in Athens, Greece, is providing statistical expertise for all the projects.

ETOP is a foundation with the purpose to promote and exchange research in the field of thoracic malignancies in Europe. ETOP still expands and consolidates its activities. During its first five years it has already become one of the leading organisations conducting research in the field of thoracic malignancies and certainly continues to grow in expertise, recognition and leadership. At the basis of this success is the determination of the ETOP investigators to collaborate in research and to openly exchange information.

ETOP projects and trials

Lungscape

Lungscape was initiated in 2011 as a result of discussion on how to foster translational collaborative research within ETOP. Its objective was to develop a decentralised biobank of tumor samples with centrally collected extensive annotated clinical data as a resource for the description of the landscape of molecular changes in non-small cell lung cancer, the generation of hypotheses regarding the prognostic impact of specific markers in patients with complete resection of non-small cell lung cancer and the generation for future diagnostic platforms and biomarker driven clinical trials.

The aim was to perform biomarker testing where feasible at the participating site after external quality assurance. Biomarkers are to be tested sequentially as funding becomes available. An unrestricted grant from Roche and a grant restricted to testing ALK in adenocarcinoma were obtained by the end of 2011 and the Lungscape master protocol and Lungscape 001-ALK substudy were distributed in May 2011 and activated in the individual sites over the following 12 months. In its initiation, Lungscape included 14 sites from Europe, subsequently a site from China and from the USA and in 2013 one additional site from Europe have joined the effort. Data on more than 2700 patients have been included in the database.

ETOP 2-11 BELIEF

BELIEF, the first therapeutic trial sponsored by ETOP is chaired by Rafael Rosell and Rolf Stahel and is being coordinated by the Spanish Lung Cancer Group (SLCG). Oliver Gautschi is co-chair of this trial. BELIEF aims at determining the long-term outcome of patients with advanced NSCLC and activating EGFR mutations (deletion of exon 19 and L858R) treated with erlotinib and bevacizumab. Notably, one of the objectives of the trial is to assess the clinical relevance of the EGFR T790M mutation in a prospective way.

Until 30 June 2014, 92 of the planned 102 patients have been recruited from 6 countries; SAKK sites have enrolled 34 patients. The accrual goal will be reached this summer.

ETOP 3-12 EMPHASIS-lung

The predictive value of a proteomic signature, called Veristrat, regarding erlotinib efficacy is being assessed in this trial in pretreated advanced squamous cell lung carcinoma. Over 50 centers from several European countries were activated. Until the end of January 2014, 81 patients were randomised, 14 from SAKK sites. Recruitment was terminated prematurely due to an accrual rate. No safety concerns led to the decision to close accrual. Treatment and follow-up of all included patients continue as specified in the protocol. The trial results will be evaluated and published.

ETOP 4-12 STIMULI

Thirty percent of patients with small cell carcinoma (SCLC) will have limited stage disease, with a median survival of 16 to 24 months with current forms of treatment and only 15-25% long term survivors.

The primary objective of the randomised multicenter open-label STIMULI trial is to evaluate if limited-disease SCLC patients treated with standard chemo-radiotherapy and prophylactic cranial irradiation followed by ipilimumab consolidation have a better overall survival compared to patients treated with chemo-radiotherapy and prophylactic cranial irradiation alone. Overall survival is

the primary endpoint, the hypothesis of interest being an absolute increase of 12.3% in OS rate at 2 years with ipilimumab consolidation treatment.

A large immune-based and immunomonitoring translational research program is planned within ETOP specialised centers and in collaboration with the Ludwig Institute in Lausanne.

The protocol has been sent out to the two SAKK sites who will participate, as well as to sites in Spain, France, Germany, Belgium, Poland and the UK. The activation process is ongoing and the first patient was enrolled in July.

ETOP 5-12 SPLENDOUR

In a pivotal phase III trial in patients with NSCLC and bone metastasis, the effect of denosumab on time to first on-study skeletal-related event relative to zoledronic acid by tumour stratification factors resulted in a hazard ratio (HR) of 0.84 for NSCLC (95% CI, 0.64 to 1.10; P=0.20). Interestingly, an ad hoc analysis examining overall survival for specific distinct strata, demonstrated a significantly improved overall survival in NSCLC patients treated with denosumab compared to reated with zoledronic acid with a HR of 0.79 (9.5 vs. 8.1 mos., 95% CI, 0.65 to 0.95).

SPLENDOUR is an ETOP-sponsored open-labeled multicentre randomised phase III prospective trial to evaluate the potential of denosumab – as an antitumor agent – to increase survival of advanced NSCLC with or without bone metastasis, when combined with platinum-based first line standard chemotherapy. The trial will be conducted in the context of a strong and unique European collaboration between ETOP and the EORTC, which will act as the coordinating group. 1000 patients will be enrolled within about 3 years.

The protocol plans the systematic collection of tissue and serum samples from all enrolled patients. Tissue blocks will be stored centrally at the ISREC in Lausanne and will be evaluated for biomarkers on the efficacy of denosumab and will constitute a unique source for further exploratory analyses. Sequential serum samples will be sent to the biorepository of the Northern General Hospital Sheffield and will undergo an array of biomarkers like CTX, osteoprotegerin (OPG), bone sialoprotein (BSP), osteopontin (OPN), free RANKL and RANKL-OPG. These may be changed and the panel of serum biomarkers will include best candidates at the time of analysis.

The protocol will be activated soon across Europe. The survey conducted at the end of last year has raised a lot of interest and about 150 sites and several cooperative groups, especially CECOG, GFPC and SLCG, have applied for participation. The total number of sites is limited; the good news is that nine SAKK sites will be able to participate. An investigator meeting specifically for SAKK sites was held during the SAKK semi-annual meeting on June 26.

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«Is there a Future for Swiss Academic Clinical Research?» 5th Symposium of the Swiss Clinical Trial Organisation (SCTO) Bern, June 18, 2014

Tatiana Terrot, Project Manager, Clinical Trial Unit, Ente Ospedaliero Cantonale, Bellinzona

On June 18th, 2014 the 5th Symposium of the Swiss Clinical Trial Organisation (SCTO) was held at the University Hospital of Bern.

The SCTO is a non-profit organisation that aims at supporting patient oriented clinical research in Switzerland. The organisation, which has been active in this field since 2009, coordinates and harmonises the activities of the 6 Swiss Clinical Trial Units (CTU). As central cooperation platform, the SCTO strives to promote a high-quality and nationally harmonised study culture to attractively and competitively position Swiss clinical research in international competition. Furthermore, the SCTO aims at building bridges between academia, industry and public authorities, while facilitating the communication among all stakeholders.

Members of the SCTO are the five Swiss University Hospitals, the St. Gallen Cantonal Hospital, the Swiss Academy of Medical Sciences (SAMW) and the representatives of the medical school faculties (Collège des Doyens) at the Swiss universities.

«**Is there a Future for Swiss Academic Clinical Research?**» was the topic of the 5th Symposium of the SCTO, a topic always in discussion and which involves not only researchers but also politicians and pharmaceutical companies.

Clinical research is very active in Switzerland and most of it is supported by the pharmaceutical industry. In the last years, thanks to the support of the CTUs, academic clinical research has become more and more active and has been able to provide high quality and expertise to the trial design, implementation and data analysis.

Academic clinical research in Switzerland is supported mostly by national and private funding. One of the aims of this Symposium was to discuss the conditions created by the new regulation (Human Research Act, HRA), introduced in January 2014, in terms of improvements and drawbacks of the academic clinical research in Switzerland. During the Symposium several speakers discussed this topic from different points of view: Dr. François Jaquet, Head of Division Clinical Trials, Swissmedic, gave a short summary on the new Swiss law and ordinances related to the human research; Prof. Christiane Pauli-Magnus and Prof. Mirjam Christ-Crain, Dep. Clinical Research University Hospital Basel, presented the positive effects of the new law by a case study; Prof. Stephan Windecker, Department of Cardiology, University Hospital Inselspital Bern, showed, on the contrary, the negative aspects of the implementation of the Swiss Ethics Committee's new organisation in a provocative talk; Hansruedi Völkle, a patient, presented the expectations from a patient perspective.

The new law on research involving human beings (Human Research Act, HRA) aims mainly to shorten time until Regulatory Authorities approval introducing the parallel submission of a new clinical trial to Swissmedic and the Ethics Committee. This is now possible as the responsibilities of the Regulatory Authorities have been clarified and redundancies were eliminated. To maintain high quality of the clinical research, Swissmedic increased the number and the scope of inspection visits. As mentioned, the main advantage of the new law consists in the parallel submission process, whereby the Ethics Committees are still in the preparation phase and establishment of a better organisation among them. From the researcher's point of view, it seems that the communication among these committees is not efficient yet. Templates are continuously updated and, after 6 months, they need further updating. In this sense, the new law intends to create favourable conditions for research involving human beings; however, the current bureaucracy so far reduces this first principle and compromises a competitive trials approvals procedure with other countries.

What do patients think about clinical research? Clinical research brought huge progress in patients' treatment over the past 30 years and difficult diseases like HIV can today be easily controlled allowing the patients to lead an almost normal life. Patients' expectations regarding clinical research include an improvement of the quality of life with fewer side effects of the treatments as well as a longer life expectancy. But patients also want to be more involved in clinical research, for example by being more considered and more informed of the results. Furthermore, patients demand greater collaboration between clinical and social research to receive better care.

The second part of the 5th Symposium started with a nice entertainment by Thomas Fraps, a magician who amused

the audience in the role of a fake expert. After a smooth restart, the second part of this event dealt with funding strategies for clinical research of other countries. The funding schemes of the German Research Foundation (DFG) and the Research Council of Norway were presented and the experiences of a reorganisation of the Italian clinical research funding, carried out 10 years ago, were shared. Researchers highlighted their experience in the funding of their clinical studies in Switzerland.

Clinical research in Germany is very complex because of different stakeholders with different interests. Because of this complex organisation the quality of clinical research is often not as expected and is lower than international standards. Only few studies are published. DFG is an independent private organisation, which aims to provide funding to selected research projects. There is not a specific field of interest: a project must have a scientific and non-marketed interest and must be a multicentre study in order to be selected. The economic situation in Germany discourages clinical researchers because of the pressure due to the high costs and limited time to dedicate to this activity. The DFG's strategy is «where they fund and not how much is invested». In contrast, Norway has four health regions with state-owned Regional Health Authorities, responsible for ensuring specialised health services for the public and for funding clinical research projects. Among the Norway University Hospitals, clinical research is supported by a network and a long term program has been established focusing on multiregional, national and international intervention studies, as well as research in the field of general practice and primary health care services. The collaboration of the four regions is important also to maintain national competition. In Italy, instead, there wasn't an independent research funding program until 2003. The research was driven and financed mainly by pharmaceutical companies and public funding was very poor. In 2003 the «Agenzia Italiana del Farmaco» (AIFA) was established to force the pharmaceutical companies to support the public funding by providing 5% of their annual income. Unfortunately the research program was frozen for political reasons in 2008 and since then public funding has been difficult to obtain. An interesting funding experience was done in a multicentre study, involving Switzerland, France and Germany, on deep brain stimulation in the early phase of Parkinson's Disease. Two independent groups, one in France and one in Germany, designed a similar clinical trial and being aware of this, decided to start a collaboration. Because of the different languages and cultures of the groups, and different countries' regulations and requirements, many obstacles had to be overcome. Not only the administrative aspects of study implementation were demanding; the search for funding was also a long path. The clinical trial costs' coverage was possible thanks to public and pharmaceutical company funding.

Prof. Peter Jüni, ISPM and CTU Bern, concluded the presentations of this Symposium by highlighting the problem of the cost coverage of academic clinical research in Switzerland. In the latter country, clinical research receives public funding through the Swiss National Science Foundation (SNSF). This is generally not enough to support all independent research projects. To cover the costs of a clinical trial more sources of funding need to be considered. This type of funding is however difficult to manage, as pharmaceutical companies are not interested in independent research. A new scheme of funding should be evaluated possibly in conjunction with public health insurances and pharmaceutical companies.

The 5th Symposium closed with a round table discussion on different perspectives of academic clinical research and funding schemes with the participation of David Nadal (SwissPedNet), Dr. Peter Brauchli (Swiss Group for Clinical Cancer Research, SAKK), Dr. Yvonne Gilli (National Council, Grüne), Dr. Andreas Schiesser (santésuisse), Dr. Aysim Yilmaz and Prof. Urs Frey (both Swiss National Science Foundation, SNSF). The discussion raised several problems, from the difficulties in getting funding independent research to the poor coordination among researchers. Furthermore, the political landscape is not sufficiently sensitised on this topic and, therefore, more efforts should be done in order to increase awareness in the Parliament. Pharmaceutical companies would be interested in funding the research but, in return, they would probably like to have something and at the moment politics is not interested in starting a discussion on this issue. With the new law, more favourable conditions have been implemented but more can yet be done. For example, the financing system of off-label drugs should be revised by encouraging and facilitating their use especially in some critical fields like paediatrics and oncology.

All participants agreed that a different funding scheme should be considered. Health insurances should be more involved by actively contributing to the academic clinical research. Collaboration and better communication among all stakeholders (politicians, pharmaceutical companies, health insurances, organisations, researchers and public) are of outmost importance as academic research is a vital social duty, necessary to answer scientific issues and patients' needs.

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deso Deutschsprachig-Europäische Schule für Onkologie

19. Internationales Seminar «Palliativbetreuung von Tumorkranken»

30. April – 02. Mai 2015, Kartause Ittingen, Warth b. Frauenfeld / Schweiz
Für Pflegende, Ärzte und weitere Interessierte

Seminarziele und -Leitung:

- Interdisziplinäre und interprofessionelle Auseinandersetzung mit fachspezifischen, gesellschaftlichen und gesundheitspolitischen Aspekten im Kontext Palliative Betreuung
- Förderung der wirksamen, interdisziplinären Zusammenarbeit und Kommunikation
- Aufarbeitung ausgewählter Aspekte aus der Symptomkontrolle sowie der psychosozialen und seelsorgerlichen Begleitung in der Palliativen Betreuung
- Reflexion moralisch-ethischer Aspekte in der Palliativen Betreuung

Dr. Agnes Glaus, PhD, Pflege-Expertin, Tumor- und Brustzentrum ZeTuP, St. Gallen (CH)
Dr. med. Daniel Büche, Palliativzentrum, Kantonsspital, St. Gallen (CH)
Dr. med. Gerda Hofmann-Wackersreuther, Palliativstation, Klinikum Nord, Nürnberg (DE)
Ulrich Oechsle, Theologe, Logotherapeut, Existenzanalytiker, eigene Praxis, Nürnberg (DE)
Prof. Dr. med. Hans-Jörg Senn, Tumor- und Brustzentrum ZeTuP, St. Gallen (CH)
Christiane Chabloz, Dipl. Pflegefachfrau, Stiftung Diaconis, Bern (CH)

18. Internationales Seminar «Onkologische Pflege – Fortgeschrittene Praxis»

03. - 04. September 2015, Universität St. Gallen / Schweiz

Seminarziele und -Leitung:

- Wissen aus Forschung und Literatur vermehren und vertiefen
- Eigene Pflegepraxis reflektieren und mit dem existierenden Wissen vergleichen
- Erkennen, welche Veränderungen in der eigenen Pflegepraxis nötig sind

Dr. Agnes Glaus, PhD, Pflege-Expertin, Tumor- und Brustzentrum ZeTuP, St. Gallen (CH)
Monica Fliedner, MSN, Pflege-Expertin, Inselspital, Bern (CH)
Elke Irlinger, MHSc, Pflege-Expertin, Stuttgart (DE)
Mag. Irene Achatz, Universitätsklinik für Innere Medizin, Wien (AT)

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Next Generation Sequencing Conference (NGS) 2014 – June 2-4, 2014 Barcelona, Spain

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The advent of Next-Generation Sequencing (NGS) technologies has revolutionized the way genomic study is progressing. The Next Generation Sequencing Conference 2014 (NGS 2014) has been a dedicated meeting on cutting-edge approaches to the processing and analysis of NGS data. It has been hosted by the International Society for Computational Biology (ISCB) and the Centre for Genomic Regulation (CRG), in the wonderful city of Barcelona (Spain). The conference brought together bioinformatics researchers and biologists facing new high-throughput sequencing challenges, showed how current platforms can be used to address key biological questions, what is the current state of the art for data analysis, the emerging and future trends in high-throughput sequencing and their associated computational challenges. Here, we review some of the key presentations from the conference.

The meeting kicked off with ***Thomas Gingeras*** (Cold Spring Harbor Lab.) discussing how the use of NGS has resulted in new insights of Non-Coding RNAs. Dr Gingeras, highlighted some of his own experiences with next generation sequencing and the transition from Sanger sequencing; The use of NGS technology in projects like the human ENCODE (Encyclopedia of DNA Elements) underscores several under-appreciated lessons concerning the conservation and novel functions of long and short non-coding RNAs (ncRNAs). These lessons include: a) specific short ncRNA classes are enriched in micro-vesicles and used for inter-cellular communication b) the conservation of long ncRNAs between mouse and human of several transcriptional features that appear to be independent of the degree of sequence similarity and c) a multiplicity of cap modifications present on short ncRNAs. Dr. Gingeras also called out that these and other insights drawn from data sets produced with NGS platform assist in beginning to understand what is often seen as dauntingly complex but elegantly organized genomes and continue to prompt a reconsideration of the definition of a gene.

We then moved on to discuss new strategies for achieving better de novo genome assemblies from NGS, presented by ***Tyler Alioto***. When sequencing long strands of DNA, the molecules are broken randomly into smaller fragments from which reads of the DNA sequence can be experimentally produced. Algorithms can use this information to infer the original sequence through the process of «de novo assembly». Dr. Alioto began by reiterating the difficult of this task due to experimental sequencing errors and the repeated sequence regions that are present in most genomes. His team developed a «divide and conquer» strategy where all paired-end reads are re-aligned to the assembly to detect regions where mappings are inconsistent, at which they subsequently break the assembly. They join the pieces through a re-scaffolding step increasing the final contiguity. He ended his talk presenting data showing how the «divide and conquer» strategy really pays off in terms of time and efficiency.

Following Alioto was ***Rory Stark*** from the University of Cambridge to present his new algorithm ChIPQC for computing and reporting quality metrics for ChIP-Seq experiments. He reiterated the need for quality control at multiple steps of an NGS workflow, including run quality, sample quality, peak calling and interpretation.
ChIPQC offers a straightforward way to generate an interactive QC report for a sample or a set of samples associated with an experiment which can be examined to assess the absolute and relative quality of individual ChIP-seq samples as well as overall quality of the experimental data.

In a later session, ***Kristin Ardlie*** (The Broad Institute of Harvard and MIT) discussed clinical reporting based on the The Genotype-Tissue Expression (GTEx) Program, a very interesting project launched by the US National Institutes of Health (NIH) in September 2010 that aims to study human gene expression and regulation in multiple tissues. It is an NGS-Seq «tour-de-force»: RNA extracted from multiple tissues (an average of 28 tissues per person) from more than 900 individuals has been quantified with RNA-Seq experiments and blood DNA from each donor was genotyped. The data produced by the 2.5 year pilot study, have been enable studies of expression quantitative trait loci (eQTLs), alternative splicing, and the tissue specificity of gene regulatory mechanisms, and aid in the interpretation of Genome-Wide Association Studies (GWAS). GTEx is a pioneering project that uses state-of-the-art protocols for obtaining, storing and testing diverse human tissue types. The results of this study will provide valuable insights into the mechanisms of gene regulation and, in the future, its disease-related perturbations.

Day 2 was underway with an interesting talk about embryonic field of the single-cell transcriptomics by ***John Marioni*** from the Sanger-EBI Single Cell Genomic Centre. The amplification steps into the NGS protocols introduce technical noise, and Dr. Marioni proofed it through a dilution series experiments that clearly show that the degree of noise gets progressively worse as the amount of starting material gets lower. The problem is exacerbated for lowly-expressed genes. He suggested using spike-ins to quantify the variability. The strong correlation to cell cycle is another issue the single-cell sequencing has to face to. John's team demonstrated that is possible to «normalize» expression relative to the stage of the cell cycle. They examined T-cells and estimated that 27% of the variance in gene expression (GEX) is due to technical noise, and that for 42% of genes 30% variance can be attributed to the «cell cycle effect». By correcting for both two T-cell sub-populations become apparent, at different stages of differentiation. He identified cell sub-types in an elegant way using single-cell transcriptomics with the caveat that the technical noise/cell cycle effect must be taken into consideration.

After a quick break, ***Beatriz Bellosillo*** (Hospital del Mar-IMIM) presented her studies aiming to elucidate the molecular mechanisms of resistance to cetuximab-based therapy acquired by patients affected by metastatic colorectal cancer (mCRC). She collected paired tumor samples (prior and progression to treatment) from 37 patients with acquired resistance to this specific type of therapy, and analyzed them using next-generation pyrosequencing. Dr. Bellosillo and colleagues identified mutations in EGFR, KRAS, NRAS, BRAF and PIK3CA. RAS mutations were the most frequent event (40% of patients) and mostly affected exons 3 and 4, followed by mutations in PIK3CA (19%), BRAF (11%), EGFR S492R (8%) and novel mutations in EGFR ectodomain (5%). In conclusions multiple mechanism are responsible for acquired resistance to cetuzimab-base therapy in mCRC. This data established the need to routine molecular studies at disease progression to individualize further therapeutic decisions.

We then moved on to discuss the landscape of RNA splicing alterations in human cancers, wonderfully presented by ***Angela Brooks*** from the Broad Institute. She has developed a computational pipeline called JuncBASE to identify and quantify alternative splicing in cancer RNA-Seq data. Through this algorithm it has been possible to identified 470 altered splicing events significantly associated with mutations in the splicing factor U2AF1, including an altered splicing event in CTNNB1. In addiction, her research group has detected splice site mutations that are associated with expression of oncogenic isoforms, including isoforms of MET and ERBB2. To distinguish between cancer-specific splicing alterations and normal transcriptome variation, they have utilized RNA-Seq data from healthy individuals from the Genotype-Tissue Expression (GTEx) project. To identify splicing events that may be novel somatic driver alterations, these events have been profiled using RNA-Seq data from the Cancer Cell Line Encyclopedia and are being used as biomarkers to identify genetic vulnerabilities in high-throughput shRNA screens. Her work has a significant impact on our understanding of the role of splicing in cancer pathogenesis.

Cornelia M. Van Duijn (Erasmus MC) ended the meeting talking about the Erasmus Rucphen Family (ERF) study, a program aims to identify genetic risk factors in the development of complex disorders. She began her presentation with a brief overview of the project: 22 families that had at least five children baptized in the community church between 1850-1900 were identified with the help of genealogical records. She announced that she had recruited the living descendants of these couples getting an impressive data collection started in June 2002 and finished in February 2005 (n=2065). Dr. Van Duijn went on to detail how she is now moving over to exome-sequencing using HiSeq. In doing so, she find thousands of variants per exome, then filter these down using various approaches, and developing a new pipeline that combines the successful bioinformatics approach followed for rare disease analyses and classical genetic epidemiological analyses. The schematic of this pipeline is certainly a useful resource for researcher looking for genetic risk factors.

All in all, NGS 2014 was a fantastic and enriching 2-day conference with excellent scientific sessions. The meeting highlighted the near complete absence of bioinformatic best-practice guidelines and standardized pipelines for NGS data analysis. Despite this issue, the final statement was clear: NGS is currently used and will be used in clinical practice.

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Innovatives Konzept holt internationalen Krebskongress in die Innerschweiz

Das wissenschaftliche Steering Committee (von links nach rechts): Dr. Daniel Helbling, PD Dr. Thomas Ruhstaller, Prof. Roger Stupp, Dr. Stefan Zimmermann, PD Dr. Roger von Moos fehlt auf dem Bild (er weilt am ASCO in Chicago)

Parallel zum wichtigen internationalen Krebskongress ASCO fand auch dieses Jahr wieder das «Chicago in the Mountains» statt. Nach dem erfolgreichen Start des Projekts im 2013 hatten die Onkologen aus der ganzen Schweiz wiederum die Gelegenheit, vom 1. bis 4. Juni 2014 die wichtigsten Präsentationen des grössten Krebskongresses in einem ruhigen Berghotel in der Innerschweiz zu verfolgen und direkt vor Ort zu diskutieren. Ein Konzept, das einem echten Bedürfnis entspricht und bei den Teilnehmern auf grossen Anklang stösst.

Für Onkologen ist der ASCO einer der wichtigsten internationalen Krebskongresse, um sich über neue Entwicklungen in der Onkologie zu informieren. Der Kosten-Nutzen-Effekt einer Reise nach Chicago ist jedoch für die Ärzte nicht wirklich befriedigend. Mit jeweils über 30'000 Teilnehmern und mehreren parallelen Sessions ist der Kongress so gross, dass vor Ort nie alle wichtigen Präsentationen besucht werden können. Genau hier setzt das «Chicago in the Mountains» an.

Technik sei Dank - Flüeli-Ranft rückt ganz nahe zu Chicago

Mit modernster Technik wurden die Vorträge und Diskussionen in Chicago den Kollegen im Heimatland simultan zugänglich gemacht. Neben der Übertragung der Präsentationen vom ASCO in sogenannten «Virtual Meetings» gab es tägliche Live-Schaltungen zu einem in Chicago aufgebauten Interviewstudio. Am Kongress präsentierte Daten konnten so nicht nur verfolgt, sondern direkt mit Experten in Chicago und den eigenen Kollegen am Event bewertet, diskutiert werden. Die übertragenen Vorträge beinhalteten ASCO-Highlights, die von einem unabhängigen schweizerischen wissenschaftlichen Gremium (Steering Committee) im Vorfeld ausgesucht und dann durch in Chicago vor Ort anwesende Kollegen (Scouts) nach Qualität und Neuigkeitswert der Vorträge adaptiert wurden: die Scouts meldeten nach Besuch der wissenschaftlichen oder Educational Sessions in Chicago die Highlights der Vorträge an das Steering Committee in Flüeli-Ranft. Dieses sichtete die entsprechenden Vorträge dann oft noch spätabends oder am Morgen vor Programmbeginn, damit die Sessions noch am selben Tag den Teilnehmern präsentiert werden konnten.

Hochkarätiges Committee sorgt für unabhängige Programmgestaltung

Die fünf Ärzte des Steering Committees Dr. Daniel Helbling vom Onkozentrum Zürich, PD Dr. Thomas Ruhstaller vom Kantonsspital St. Gallen, Prof. Roger Stupp vom Universitätsspital Zürich, PD Dr. Roger von Moos vom Kantonsspital Graubünden und Dr. Stefan Zimmermann vom Hôpital de Fribourg waren allesamt bereits im 2013 mit von der Partie und zeigten sich erneut angetan von Konzept und Organisation der Veranstaltung. Stellvertretend für seine Kollegen Dr. Zimmermann: «Der Event ist rundum gelungen. Toll auch, dass so viele Ärztinnen und Ärzte den Weg hierhin gefunden haben. Ohne Zweifel entspricht die Veranstaltung einem Bedürfnis und bietet eine willkommene Alternative zur Teilnahme in Chicago. Extrem geschätzt wird von den Teilnehmern die Möglichkeit, das Beste vom ASCO mitzuerleben. Da die Sessions in Chicago oft

parallel laufen, ist 'cherry-picking' dort nicht machbar. Besonders staune ich dieses Jahr über die sehr differenzierten Fragen der Teilnehmer zu den Präsentationen und Diskussionen in Chicago - sie sind auf einem hohen Niveau, was die Sache für uns als Steering Committee noch interessanter macht.»

Global interagieren, dabei aber Umwelt schonen und Zeit sparen

Die Veranstaltung entspricht einem echten Bedürfnis, mussten die Ärzte doch nicht nach Amerika reisen, um sich über die neuen Entwicklungen in der Onkologie zu informieren. So fanden über 50 Onkologen aus Privatpraxen und Spitälern den Weg nach Flüeli-Ranft. Während drei Tagen konnten sie bequem, ganz ohne Reisestress und Jetlag, in einer entspannten und inspirierenden Umgebung den Präsentationen folgen und sie anschliessend untereinander diskutieren - ein echter Mehrwert, den auch Frau Dr. Sylvia Baumann Kurer von der Onkologiepraxis Winterthur bestätigt: «Das Chicago in the Mountains gefällt mir sehr gut. Als Mutter schätze ich es, nicht allzu lange von meinen Kindern weg zu sein. Das Programm ist vom Steering Committee sehr gut zusammengestellt und erleichtert es, sich auf eine Selektion an Themen zu konzentrieren. Daneben finde ich es grossartig, mich an diesem tollen Ort mit meinen Kollegen auszutauschen. Ein solch intensiver Austausch ist in Chicago wegen der Grösse des Kongresses nicht möglich.»

Chicago in the Mountains – Entstehung und Grundsätze

Beim «Chicago in the Mountains» wurde die Trennung von Finanzierung / Organisation und Veranstaltungsinhalten von Anfang an gross geschrieben. Die Programmgestaltung, Auswahl der Experten, Sessions und die Moderation wird vollkommen unabhängig durch das wissenschaftliche Steering Committee bestimmt. Dieses investiert jedes Jahr viel Zeit, um internationale und nationale Experten auszuwählen und zu kontaktieren, Sessions zu sichten und mit Hilfe seiner Kollegen in Chicago die Highlights auszuwählen. Eine Arbeit, die Monate vor der Veranstaltung beginnt und erst mit der Übertragung und Diskussion der letzten Session in Flüeli-Ranft beendet ist. Initiiert wurde die Veranstaltung von der Roche Pharma (Schweiz) AG im 2013. Die Roche Pharma (Schweiz) AG hat auch dieses Jahr die logistische Unterstützung der Veranstaltung koordiniert und einen namhaften finanziellen Beitrag geleistet. Um die langfristige Realisierung und Unabhängigkeit von «Chicago in the Mountains» sicherzustellen, wird ein Multisponsoring-Konzept gewählt. In diesem Jahr wurde die Veranstaltung neben Roche von Amgen und Astra Zeneca finanziell unterstützt.

F-18-DOPA PET/CT revealed a neuroendocrine tumor located in an unusual site

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms with increasing incidence, various clinical presentations, growth rates and responses to available therapies. They arise from the neuroendocrine cells which are located in different organs through the body, although most frequently NETs arise from abdominal and thoracic organs [1].
Chromogranin A is still the best available marker used for the biochemical confirmation of these tumors [2], but new more sensitive markers are urgently required. Although scintigraphy with Indium-111-octreotide has widely been applied for the localization and staging of NETs [3], newer imaging modalities based on the functional characteristics of these tumors are evolving aiming not only to facilitate the diagnosis but also prognosis and evaluation of treatment [4].
Here we report the case of a rare NET located in an unusual site detected by fluorine-18-dihydroxyphenylalanine positron emission tomography/computed tomography (F-18-DOPA PET/CT).

Case report

A 33-year-old man with progressive hearing impairment underwent a CT scan which showed an abnormal tissue in the right middle ear (Fig. 1). The patient refused the biopsy. Based on the increased serum chromogranin A value (280 U/L), the presence of a NET was suspected.
The patient underwent a F-18-DOPA PET/CT to look for a possible NET. F-18-DOPA PET/CT was performed without carbidopa premedication. Images were acquired 60 minutes after the i.v. injection of 4 MBq/Kg of F-18-DOPA.
Three-dimensional PET/CT reconstruction (Fig. 2), PET and fused PET/CT images in axial, sagittal and coronal projection (Fig. 3) showed the presence of a focal area of increased radiopharmaceutical uptake corresponding to the abnormal tissue in the right middle ear. No other areas of abnormal F-18-DOPA uptake were detected in the rest of the body.

Figure 1: Axial CT showing abnormal tissue in the right middle ear.

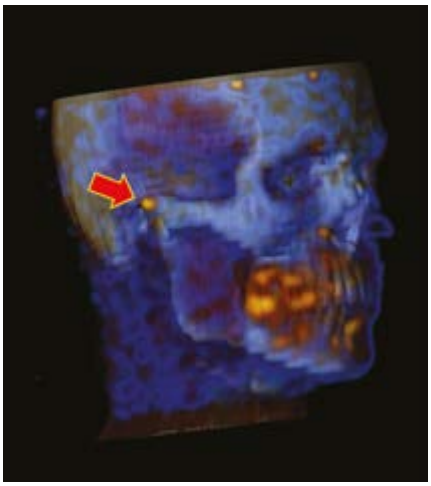

Figure 2: F-18-DOPA PET/CT three-dimensional reconstruction showing a focal area of increased tracer uptake in the right middle ear (arrow).

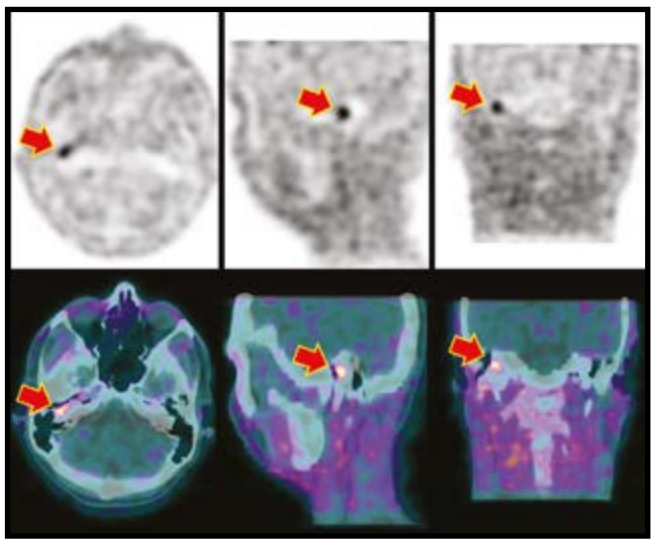

Figure 3: PET (upper row) and PET/CT images (lower row) showing a focal area of increased F-18-DOPA uptake in the right middle ear (arrow).

Based on this PET/CT finding the patient underwent surgery. Histological examination of the tissue in the right ear revealed tumor cells forming gland-like and cribriform structures at hematoxylin and eosin staining (Fig. 4A). No cellular atypia nor significant mitotic activity were found. On immunohistochemical staining, tumor cells were positive for epithelial markers such as cytokeratins (Fig. 4B), and neuroendocrine markers such as synaptophysin (Fig. 4C) and chromogranin (Fig. 4D). Based on these histological findings a diagnosis of well-differentiated NET of the middle ear was performed and the patient was addressed to follow-up.

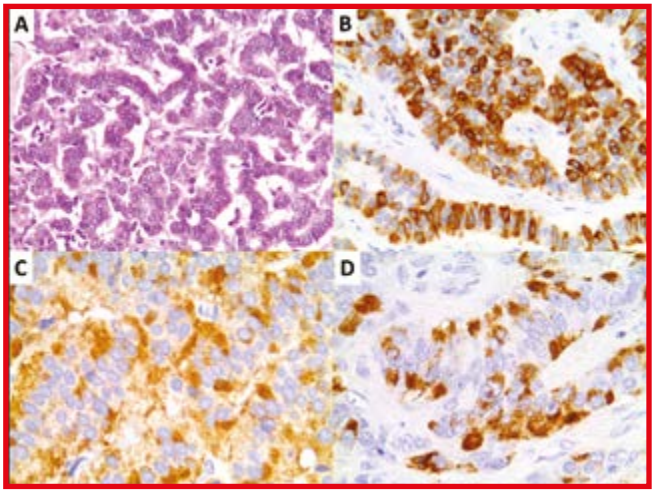

Figure 4: Histological examination of the tissue in the right ear revealed tumor cells forming gland-like and cribriform structures at hematoxylin and eosin staining (A). Tumour cells were positive for cytokeratins (B), synaptophysin (C) and chromogranin (D).

Discussion

Abdominal and thoracic regions represent the most frequent location of primary NETs. Less often patients develop NETs in the head and neck region [1]. An uncommon site of origin of NETs in the head and neck area is the middle ear. NETs of the middle ear are usually benign entities and the most frequent symptom is hearing impairment; nevertheless, in a small number of cases they may metastasize to cervical lymph nodes [5].

A specific feature of NETs is amine precursor uptake and decarboxylation; this is the rationale for using F-18-DOPA, a catecholamine precursor, as PET radiopharmaceutical for the detection of NETs [6].

Literature findings suggest that F-18-DOPA PET/CT is an accurate functional imaging method in patients with NETs [7] and in particular in evaluating patients with paraganglioma or pheochromocytoma [8] and recurrent medullary thyroid carcinoma [9]. About NETs of the thoracic and abdominal regions, F-18-DOPA PET/CT shows a higher diagnostic accuracy in patients with carcinoid tumors from the distal duodenum to proximal colon (midgut carcinoids) compared to other sites [6].

In our case F-18-DOPA PET/CT has been very useful in revealing and staging a primary NET of the middle ear, demonstrating that this functional imaging method may be useful to detect NETs located in unusual sites.

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